

it would be useful to know whether levels of factor VII and of proteins C and S influence the extremes of warfarin dosing.

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THE AUTHORS REPLY: We agree with Garcia and Hylek that it is uncertain whether genetic-based warfarin dosing will improve outcomes, and this dosing approach cannot solve the other management problems related to warfarin dosing (e.g., fragmented care). Randomized, controlled trials comparing genotype-guided care with a nongenetic approach are planned in the United States, Europe, and Korea and will be a critical step in showing that genotype-based dosing can improve anticoagulation control. Ultimately, very large trials may be needed to determine the effect of genotyping on clinical outcomes.

Nonetheless, it is not difficult to envision that genetics-guided warfarin dosing could improve important and costly outcomes, such as extra clinic and emergency room visits. Even a reduction in minor bleeding could improve a person's quality of life and decrease the need to discontinue a highly effective therapy. Our study suggests that the use of genetics might benefit nearly half the patients who are initiating warfarin therapy. Thus,

there is the potential that genetic-guided warfarin dosing could prove to be cost-effective, particularly among patients at high risk for hemorrhage. In addition, as the cost of genotyping decreases, cost-effectiveness could be further enhanced.

In response to Shil and Strohm's point about age, our algorithms do estimate lower doses in the elderly. We also agree that there are other factors, both genetic and nongenetic, that may influence warfarin dosing requirements, particularly at the extremes.

Although we do not yet have all the answers regarding the value of genotype-guided warfarin dosing in clinical practice, our study provides an understanding of its potential benefit. Like most diagnostic tests, genetic testing will not benefit all persons. Clinicians must assess the current level of evidence and decide whether to implement genetics-guided warfarin dosing in practice now, await the results of the INR-focused clinical trials to adopt this approach, or adopt it only once differential clinical outcomes have been documented. Many diagnostic tests are widely adopted in practice before differential clinical outcomes have been documented; whether this will occur with warfarin dosing remains to be seen.

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Behavioral Therapy, Sertraline, or Both in Childhood Anxiety

TO THE EDITOR: Walkup and colleagues (Dec. 25 issue)¹ conclude that the three active therapies they studied — a combination of cognitive behavioral therapy and sertraline, cognitive behavioral therapy alone, and sertraline alone — were effective treatment for anxiety in children, as compared with placebo. The authors further conclude that combination treatment had a superior response rate, as compared with active treatment alone. However, the study design invites questions. There was no treatment group in which

cognitive behavioral therapy plus placebo was used. The absence of such a group prevented the investigators from determining whether the addition of sertraline to cognitive behavioral therapy resulted in more improvement than each treatment given separately because of an additive effect of two active treatments or because of the placebo effect of adding a pill to cognitive behavioral therapy.

Furthermore, the children who were given a pill without cognitive behavioral therapy did not

know whether they were receiving an active or an inactive drug, whereas those receiving cognitive behavioral therapy plus a pill knew that they were getting an active medication. This could have increased the placebo effect of the pill in the combination group.

Can we then conclude that combined treatment was superior to individual treatments?

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1. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med* 2008;359:2753-66.

TO THE EDITOR: In the study reported by Walkup et al., it seems, if I have read the report correctly, that 58 of the children being treated for anxiety were receiving stimulant drugs. These drugs themselves can cause symptoms of anxiety.

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Dr. Birkett reports owning stock in Pfizer. No other potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: In the editorial accompanying the report by Walkup et al., Emslie¹ states, in support of randomized, controlled trials, "It appears unlikely that the majority of children with severe and persistent anxiety disorders are receiving optimal evidence-based care in the community." I do not believe that the results reported by Walkup et al. can be generalized, in that 84% of potential subjects were excluded (3066 screened, and 488 randomly assigned to a study group), making the external validity² of the findings doubtful.

The internal validity² is uncertain because there was no control for factors that contribute to the development of psychiatric disturbances in children. Although the authors control for demographic factors, diagnoses, and racial or ethnic diversity (not "the most socioeconomically disadvantaged"), there is no report of family history (marital discord, deaths, separations, or maltreatment of children by family members or others), nor is there information about the children's developmental and psychological trajectories.

This study, like others,³ may do a disservice to the care of children by conceptualizing pediatric psychiatric disorders as if they were categorical entities. Proper treatment can be implemented only when the full complexity of such disorders is understood, including developmental and family factors.⁴

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TO THE EDITOR: Walkup et al. report the percentage of patients with a treatment response that was "much improved" or "very much improved" on the Clinical Global Impression–Improvement scale. However, using a categorical outcome such as "improvement" can be misleading, and we believe that the conclusions should be interpreted with caution. Although there was a difference in responses based on this outcome, on the arguably more clinically relevant continuous measure, the 30-point Pediatric Anxiety Rating Scale, scores decreased from 18.8 at baseline to 9.8 at 12 weeks in the sertraline group and from 19.6 to 12.6 in the placebo group, an absolute difference between the groups of 12 percentage points, which was not reported as significant and is in fact consistent with the large placebo response and weak effect of antidepressants seen in previously reported studies in children. In fact, only cognitive behavioral therapy alone was better than placebo on this scale. In the absence of a change in the continuous measure of anxiety, the current findings should not be interpreted as definitive evidence of the efficacy of sertraline for the treatment of childhood anxiety.

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THE AUTHORS REPLY: In response to Rifkin and Braga: our study design was based on scientific and pragmatic considerations. We thought that there were three main choices for designing a study to evaluate the added benefit of cognitive behavioral therapy combined with sertraline: a four-group design, a two-by-two factorial design, and a five-group design that would include cognitive behavioral therapy plus placebo. We chose the four-group design primarily for reasons of ecologic validity (e.g., the active treatments would be delivered as they are in real-world settings). We rejected the two-by-two design because it would have required a group receiving sham psychotherapy, and that is difficult to develop and implement.¹ The one-by-five design was rejected as unfeasible. To detect the smallest, clinically meaningful difference in the response rate (10%) between cognitive behavioral therapy plus sertraline and cognitive behavioral therapy plus placebo would have required a substantial increase in the sample size and study duration. In the Discussion section of our article, we suggest caution in interpreting the study results, given the open nature of cognitive behavioral therapy plus sertraline and cognitive behavioral therapy alone as treatment conditions. However, the 81% response rate for cognitive behavioral therapy plus sertraline reflects what might be expected for quality cognitive behavioral therapy combined with sertraline in community settings.

In answer to Birkett: attention was paid to children who had both an anxiety disorder and attention deficit-hyperactivity disorder for patterns of symptom onset or worsening related to stimulant treatment. If such a pattern was suspected, the child's history was reviewed with the prescriber of the stimulant medication. The study steering committee then reviewed the child's history to determine whether the child was an appropriate candidate for enrollment in the study.

In response to Hoffman: the number of willing and eligible participants was 524, and of that group, 488 underwent randomization. The study results are generalizable to populations of anxious children who have clinical characteristics that are similar to those of the study sample.

We believe that the demonstrated success of randomization probably controls for the distribution of factors not assessed. That said, a number of the factors mentioned by Hoffman were assessed, and we are evaluating the moderating effects of these factors on outcomes.

In response to Bremner and Vaccarino: no matter how the data were analyzed, cognitive behavioral therapy plus sertraline, cognitive behavioral therapy alone, and sertraline alone were all statistically superior to placebo. The effect size based on the Pediatric Anxiety Rating Scale for sertraline as compared with placebo was moderate (0.45) and reflects the differences noted by Bremner and Vaccarino. As is consistent with contemporary scientific approaches, the primary outcome was the treatment response as indicated by the score on the Clinical Global Impression-Improvement scale and was reported as such. We believe that this scale is a meaningful index of the primary outcome. However, we are examining a wide variety of secondary outcomes.

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C3 Polymorphisms and Outcomes of Renal Allografts

TO THE EDITOR: Varaganam et al. (Feb. 26 issue)¹ do not confirm the previously reported association between the complement component 3 (C3) SS genotype and worsened outcomes of renal transplantation.² However, the disparity in the results

of these two studies may be due to differences in the proportion of recipients with specific risks of chronic allograft dysfunction. Moreover, the C3 SS genotype can be either a protective factor¹ or an exacerbating factor in the progression of endog-