less than originally planned. Landry and Oliver propose a three-group trial (norepinephrine alone, vasopressin alone, and the two combined), which raises two concerns. First, the sample-size requirements for three-group trials are onerous — much greater than those for two-group trials. Second, treating patients with vasopressin alone would be difficult because norepinephrine is used routinely as the standard of care.[5]

Mogyorosi asks about the rate of hyponatremia in VASST. Hyponatremia was recorded only if it was considered to be a serious adverse event, so the rate reported (0.3%) does not represent all cases of hyponatremia. Nonetheless, we found it reassuring that severe hyponatremia in the vasopressin group was extremely rare and was not more frequent than in the norepinephrine group. We did not use an algorithm for hyponatremia; fluid and electrolyte levels were managed by clinical teams at each center.

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Five Genetic Variants Associated with Prostate Cancer

TO THE EDITOR: We agree with Zheng et al. (Feb. 28 issue)[1] that additional research is needed to assess the value of their finding of genetic variants associated with the risk of prostate cancer. Unfortunately, the planned marketing of a test based on this study[2] is premature and may cause more harm than good. Finding a genetic association is only the first step in the continuum of translating research into practice.[3] The results have not been independently confirmed, and adding the genetic test results to age, region, and family history only marginally improved risk prediction (the area under the curve [AUC] increased from 0.61 to 0.63). The clinical utility of the test is questionable because it cannot be used to reduce risk, since there are no known modifiable risk factors[4]; to encourage screening, since the balance of benefits and harms is unknown[5]; or to predict the clinical course of the disease, since the variants were associated equally with aggressive and nonaggressive cancers.[1] In the absence of evidence of improved outcomes, this test may lead to unnecessary or potentially harmful procedures.

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TO THE EDITOR: In his accompanying editorial, Gelmann states that the five polymorphisms reported by Zheng et al. do not yet constitute a viable screening test.[1] We think they never will. The use of genetic polymorphisms with modest odds

Table 1. Performance of a Screening Test for Prostate Cancer Based on Six Risk Factors (Five Genetic Polymorphisms plus Family History).

Test Cutoff (no. of risk factors)	Detection Rate (sensitivity)	False Positive Rate (1 – specificity)	Positive Predictive Value	Negative Predictive Value
		percent		
≥1	95.02	89.93	63.89	54.72
≥2	68.13	56.31	66.95	45.02
≥3	31.73	20.31	72.34	41.08
≥4	9.54	3.76	80.94	38.86
≥5	1.38	0.29	88.89	37.65

ratios (1.22 to 1.53 in the study by Zheng et al.) to screen for a polygenic disease such as prostate cancer is unlikely to be practical because most men, whether or not they have prostate cancer, will be at average genetic risk.[2] In the study by Zheng et al., most case subjects and control subjects had one to three risk factors (85.5% of case subjects and 86.2% of control subjects), and less than 10% of the case subjects were at high risk. A test based on these polymorphisms cannot distinguish adequately between case subjects and control subjects and will miss most cases or have false positive results for most controls (Table 1). This is reflected in the very poor AUC of the receiver-operating-characteristic curve even when these genes are combined with other risk factors (AUC, 0.63), which is not much better than that which is expected by chance (AUC, 0.50).

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TO THE EDITOR: Zheng et al. report that the combined effect of family history and five single-nucleotide polymorphisms (SNPs) on the risk of prostate cancer was increased by a factor of 9.46 for men who had at least five factors as compared with those who had none. This contradicts the low discriminative accuracy they observed (AUC, 0.63). For the calculation of this odds ratio, they compared the relatively small highest-risk category with the lowest-risk category. Selection of the lowest-risk category as the reference is a frequently used and powerful approach to demonstrating an association,[1,2] but it does not give a realistic impression of the clinical usefulness of the findings. To evaluate the increase or decrease in the risk of disease as compared with the pretest or overall risk, we have recalculated the odds ratios, shown in Table 4 of the article, for number of associated factors as follows: no associated factors, 0.49 (observed in 10% of the controls); one factor, 0.80 (34%); two factors, 1.01 (36%); three factors, 1.34 (17%); four factors, 2.35 (3%); and five or more factors, 4.78 (<1%). Although the findings of Zheng et al. are of great interest, their AUC analysis and a simple recalculation of their data show that the clinical implications are limited.

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TO THE EDITOR: The claim by Zheng et al. that five SNPs plus a family history "account for" 46% of cases of prostate cancer is misleading. They invoked the concept of population attributable fraction (PAF), not population attributable risk, as they incorrectly called it. PAF approximates the proportion of disease prevented by eliminating a risk factor.[1] Its application to genetics is questionable.

None of the variants are known to be causal; elimination of the variants, even if possible, would not necessarily prevent prostate cancer. In any case,

PAF is highly dependent on the reference group.[1] A broader definition than the authors' choice of men with no risk alleles (10% of controls) would lead to a lower PAF.

A better gauge of the effect of measured genes on a disease is the extent to which they explain the increased risk associated with having an affected first-degree relative.[2] With adjustment for the SNPs, the family-history effect went from 2.26 (Table 1 of the article by Zheng et al.) to 2.22 (Table 4 of the article), so they explained just 2% of familial aggregation.

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TO THE EDITOR: Large-scale genomewide studies[1] have identified risk alleles with low odds ratios that can have little clinical utility for risk prediction. Zheng et al. combined genotypes to see whether the odds ratio can be increased to clinically useful levels for estimating the risk of prostate cancer. However, the authors did not compare the performance of the combined genotype with the current standard, prostate-specific antigen (PSA). Approximately 20% of their case subjects had a family history of prostate cancer, and 90% had a PSA level of more than 4 ng per milliliter; combining the two would probably have given a similar, if not better, population attributable risk. The addition of the combined genotype to age, region, and family history improved the AUC by a mere 3%, indicating lack of meaningful improvement over current methods. Finally, as with CHEK2 in breast cancer,[2] the odds ratio is too low to be useful at such a low prevalence of the combined genotype. An increase in the odds ratio obtained by combining genotypes comes at the price of a decline in the prevalence of the combined genotype.

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TO THE EDITOR: The model of Zheng et al. has limited predictive ability: using the data in Table 4 of their article, we estimate an AUC of 0.57 for the SNPs. This is dwarfed by the AUC for a single PSA test at 44 to 50 years of age: in a large study of a representative, unscreened population, we reported an AUC of 0.76 for the occurrence of prostate cancer up to 25 years subsequently.[1] Moreover, we have shown[2] that a single PSA test can accurately predict advanced prostate cancer (AUC, 0.79) and that screening decisions based on a single PSA test before the age of 50 years are likely to lead to better outcomes for patients than the competing alternative strategies of screening all or no men.[3] As such, the proven technology of PSA testing currently offers by far the best method of stratifying men according to risk for prostate-cancer screening.

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Drs. Vickers, Lilja, and Scardino report holding patents for assays of free PSA and human glandular kallikrein 2. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: According to the data of Zheng et al., it could be expected that if very few persons have none of the six risk factors they report (about 4%), then about 19% of the population

will have only one risk factor. On the basis of the hypothetical mean lifetime risk of prostate cancer of 10%, men with no risk factors might have less than a 4% lifelong risk, and men with only one risk factor less than a 6% lifelong risk. For these subgroups, the benefit of screening in relation to the risk is even more doubtful than it is in the general population.

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THE AUTHORS REPLY: Our finding of a cumulative effect of five genetic variants and family history on the risk of prostate cancer in a population-based case–control study in Sweden was recently confirmed in two U.S. populations.[1] The consistent finding of a strong cumulative effect on prostate-cancer risk, together with a relatively high frequency in the general population, calls for a new perspective in the interpretation and use of genetic information.

Until a perfect biomarker for predicting prostate-cancer risk is available, there is a need to search for biomarkers that individually or collectively offer some utility for risk prediction. We emphasize that our approach represents an initial but important step toward this goal. We found that a cutoff of three of these six risk factors had a specificity of 80% and a sensitivity of 32% for discriminating between case subjects and control subjects in this Swedish population. Although its specificity is lower than that of PSA (94%) with the use of a cutoff of 4.1 ng per milliliter, its sensitivity is higher than that of PSA (21%).[2] With 10 additional risk variants reported since February 2008, it is expected that the sensitivity and specificity will be further improved.

We do not advocate replacing the PSA test with genetic tests; we envision combining these tests to improve their predictive ability. Although we could not assess joint discriminatory performance because of our study design, we found that the cumulative effect of genetic risk factors is independent of PSA levels and thus can provide complementary information.

Just as men with a family history of prostate cancer are encouraged to start undergoing screening at an earlier age, men with multiple genetic risk factors might similarly be encouraged to begin screening earlier. Unlike family history, which is subject to the limitations of family size, structure, current age of male relatives, and reliability of reporting, genetic markers can be accurately measured anytime.

Although it is difficult to provide risk information with confidence for most men (who carry one, two, or three of the five genetic risk factors) by means of genetic markers alone, men who are at the two extremes in terms of the number of inherited factors may benefit substantially from categorization of their risk for prostate cancer.

Additional studies, especially prospective ones, are needed to further improve prediction of prostate-cancer risk by including additional risk variants, combining them with PSA and other detection methods, and incorporating genetic markers that distinguish aggressive from nonaggressive prostate cancer in order to predict disease progression.

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Since publication of the article, Dr. Xu reports founding Proactive Genomics, a company that will offer genetic testing for predicting individual prostate-cancer risk. No other potential conflict of interest relevant to this letter was reported.

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Genetics of Warfarin Response

TO THE EDITOR: In the study reported by Schwarz et al. (March 6 issue),[1] specific genetic variants related to warfarin metabolism reduced the time to the first therapeutic and supratherapeutic international normalized ratio (INR) tests. A pharmacogenetic-guided dosing algorithm for warfarin,[2] however, did not increase the time in the therapeutic range or reduce the proportion of su-