Editor's note: Drs. Lassen and Borris have served as consultants to Knoll and other companies that develop antithrombotic compounds. Dr. Nakov was an employee of Knoll.

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2. Chan LY, Yuen PM, Lo WK, Lau TK. Symptomatic venous thromboembolism in Chinese patients after gynecologic surgery: incidence and disease pattern. Acta Obstet Gynecol Scand 2002;81:343-6.

Cyclin E in Breast Cancer

TO THE EDITOR: Keyomarsi et al. (Nov. 14 issue)[1] present the exciting and powerful finding that the levels of cyclin E in breast-cancer cells, as measured with the Western blot assay, correlate strongly with prognosis; however, there is a potential problem with their methods. The authors state, "Densitometric values for actin were used to standardize for equal protein loading." Are they aware that benign components of breast tissue such as myoepithelial cells have much higher actin levels than cancer cells? Many breast-cancer tissues will have some mixed benign component. A potential pitfall of using actin is that proteins from cells of less dense tumors (potentially lower-grade tumors) are compared with proteins from cells of denser tumors (potentially higher-grade). Such a comparison will result in artificially high measurements of cyclin E levels in higher-grade tumors. Could this problem also explain the discordance between the results of immunohistochemical analysis and those of Western blotting?

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1. Keyomarsi K, Tucker SL, Buchholz TA, et al. Cyclin E and survival in patients with breast cancer. N Engl J Med 2002;347:1566-75. [Erratum, N Engl J Med 2003;348:186.]

TO THE EDITOR: Keyomarsi et al. report that the cyclin E level was even better at predicting the prognosis than factors that are usually accepted as major prognostic factors for breast cancer, but one such factor was not studied in their article: the grade of the tumor. Information on this characteristic is routinely provided by pathologists, who usually assess it according to the Scarff–Bloom–Richardson classification or its revised version.[1] In addition, young age has been reported to be an adverse prognostic factor.[2] In the report by Keyomarsi et al., the population of patients was divided in two: those less than 50 years of age and those 50 years of age or older. We believe it could be interesting to conduct a study of cyclin E levels specifically in a population of patients who are younger than 35 years of age in order to validate this observation.

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1. le Doussal V, Tubiana-Hulin M, Friedman S, Hacene K, Spyratos F, Brunet M. Prognostic value of histologic grade nuclear components of Scarff-Bloom-Richardson (SBR): an improved score modification based on a multivariate analysis of 1262 invasive ductal breast carcinomas. Cancer 1989;64:1914-21.
2. Albain KS, Albred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? In: Breast cancer in younger women. Journal of the National Cancer Institute monographs. No. 16. Bethesda, Md.: National Cancer Institute, 1994:35-42. (NIH publication no. 93-03559.)

TO THE EDITOR: The article by Keyomarsi et al. gives no information regarding subsequent adjuvant therapy. Since the samples were obtained between 1990 and 1995, it is likely that many of the women received systemic treatment. Thus, it is possible that low cyclin E levels identify the women who will benefit most from adjuvant chemotherapy or hormonal therapy. Perhaps the authors meant that women with high cyclin E levels had a poor prognosis even when they were given adjuvant therapy, and such women "receive toxic systemic treatment with little benefit." If this were true, the cyclin E levels could be used to identify women who needed more effective regimens but not to identify women who had a favorable prognosis and could avoid treatment.

It also seems unlikely that the study of cyclin E levels in current or future prospective trials will verify the clinical usefulness of this factor. Trials of adjuvant therapy in patients with breast cancer no longer include an untreated control group. Further study involving well-characterized retrospective banks of tumors obtained from treated and untreat-

ed patients will be necessary to determine whether cyclin E is prognostic of the outcome or predicts the benefits of adjuvant therapy.

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TO THE EDITOR: In Table 1 and the figures in the article by Keyomarsi et al., the five-year disease-free survival rate is higher than the five-year overall survival rate in all subgroups analyzed. I suspect that this was a typographical error, since such a finding would be very unusual for survival curves in a study of patients with breast cancer followed after primary therapy.

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THE AUTHORS REPLY: We concur with Dr. Kang that tumors contain a variable amount of benign breast tissue, although the correlation with the tumor grade is not certain. Expression of actin is regulated by the cell cycle, and consequently, levels are more likely to be elevated in tumor cells, in which the cell cycle is, by definition, deregulated. In our experience, actin levels in normal tissues are always significantly lower than those in tumor tissue. Therefore, contamination of the tumor sample with benign tissue is not likely to have a notable effect on the actin level of the sample or to jeopardize the equal loading of samples on the Western blot assays. Finally, we also used Ponceau staining in all of our Western blot assays as an additional test to confirm equal loading.

Data regarding the prognostic value of the tumor grade in patients with small, node-negative tumors — a characterization that applies to a substantial proportion of our study cohort — are not consistent.[1-3] In fact, variability in the literature on tumor grade and prognosis led the Breast Task Force of the American Joint Committee on Cancer (AJCC) to exclude this variable from the recent AJCC update on breast-cancer staging.[4] Because of these issues of reliability and clinical utilization, we elected not to compare the tumor grade with cyclin E levels. There were 16 patients younger than 35 years of age, who were equally divided between the group with tumors that had low expression of cyclin E and the group with tumors that had high expression of cyclin E. As in the overall cohort, patients in the subgroup with low cyclin E levels had significantly better survival than those in the subgroup with high cyclin E levels (five-year disease-specific survival, 75 percent [95 percent confidence interval, 31 to 93]) vs. 25 percent [95 percent confidence interval, 4 to 56]; P=0.04).

In response to Dr. Rabinowitz, the data on survival are correct as published. The data presented are for disease-specific survival, not disease-free survival. With a median age of 64 years, many of the patients in this study died of unrelated causes; hence the overall survival rate was lower than the disease-specific survival rate.

Approximately two thirds of the patients in this series received either chemotherapy or hormonal therapy. Broadly analyzed, the level of cyclin E expression did not appear to predict the response to treatment. We are currently investigating whether the cyclin E level may predict the response to systemic therapy in specific subgroups of patients.

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Editor's note: Dr. Keyomarsi holds U.S. patents 5,543,291 (method of detecting carcinoma) and 5,763,219 (cyclin E variants and use thereof).

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Skin Ulcers Misdiagnosed as Pyoderma Gangrenosum

TO THE EDITOR: Weenig et al. (Oct. 31 issue)[1] stress the need for extensive investigations in cases of skin ulcers that are suggestive of pyoderma gangrenosum. However, their recommendation of colonos-