modifiable through quality-improvement efforts, are important determinants of outcomes in this population. In addition, the potential benefits associated with prompt defibrillation are actually large when absolute differences in survival to hospital discharge are considered: 39.3% for patients treated within 2 minutes as compared with 22.2% among those treated later (i.e., a number needed to treat of 6) (Table 1, previous page).

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THE EDITORIALIST REPLIES: Chretien takes exception to my comparison of survival rates between patients with in-hospital cardiac arrest and those with out-of-hospital cardiac arrest. He suggests that my comments provide fodder for inappropriate media attention to the issue. In one sense, he is right. I was quoted by the *New York Times* as saying that I was more likely to survive a cardiac arrest in Nordstrom's (where I happened to be standing at the time of the interview) than in some hospital settings.[1] However, I believe that media attention to this issue is not only appropriate but also necessary and positive. Hospitals and physicians are responsible for resuscitating patients after arrests from ventricular tachycardia or ventricular fibrillation in the timeliest way possible. Technologies that reduce delays in defibrillation, such as automated detection algorithms and AEDs, do exist and have been validated in out-of-hospital settings. Why not adopt these technologies and processes for hospitalized patients? There is nothing wrong with the media spotlight if it brings attention and pressure for positive change.

Chabbouh and colleagues agree that automated algorithms help identify patients in distress earlier and that AEDs should play an important role in in-hospital defibrillation. In fact, Ali and colleagues have used AEDs in the hospital setting, improving survival, and continue to work to reduce defibrillation times. I apologize for not citing their work in my editorial.[2] Finally, Bassan wonders whether aggressive and potentially costly efforts to reduce defibrillation times for all hospitalized patients will produce meaningful survival benefits. Rationing resuscitation attempts for hospitalized patients who have ventricular tachycardia or ventricular fibrillation without advance directives is nihilistic and pessimistic. If prompt resuscitation is feasible in a casino and an airport, we can do it in a hospital. In general, people are capable of understanding that survival of hospitalized patients will not be as favorable as survival of those with an arrest in a public place. Our responsibility as physicians lies with giving each individual patient the best chance at survival, and that means early defibrillation with the best technologies available.

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Breast-Cancer Stromal Cells with *TP53* Mutations

TO THE EDITOR: Patocs et al. (Dec. 20, 2007, issue)[1] report a frequency of *TP53* mutations in fibroblasts associated with sporadic breast carcinoma of 27.4%, and they show that mutation status is associated with regional nodal metastasis. If confirmed, this finding would represent an important discovery.

We sought to confirm their findings by direct sequencing of exons 4 through 9 of *TP53* in microdissected areas of stroma (<5 mm from the epithelial cancer interface) from 10 fresh-frozen sporadic breast-cancer specimens and 7 primary breast-carcinoma–associated fibroblast cultures.[2,3] No mutation was detected in any of these 17 sam-

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ples. The reason for this discrepancy is unclear, although we note that Patocs et al. used DNA derived from formalin-fixed, paraffin-embedded tumor tissue, which is notorious for generating polymerase-chain-reaction (PCR) artifacts.[4]

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Dr. Polyak reports receiving consulting fees from Novartis, Pfizer, and AVEO Pharmaceuticals, holding stock in AVEO Pharmaceuticals, receiving lecture fees from Biogen Idec, and receiving grant support from Novartis and Biogen Idec. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Patocs et al. report *TP53* mutations in breast-cancer stromal and epithelial cells. The pattern of these mutations is very unusual, since the frequency of *TP53* mutations in sporadic breast cancer was 54%, as compared with 20% in the literature,[1,2] and the frequency of tumors with double mutations was exceptionally high (23%, vs. 1 to 2%). In addition, several mutations have not previously been described — for example, the Pro89Ser mutation identified in 21 samples in the study by Patocs et al. has never been reported among the 3000 sporadic and familial breast carcinomas included in the universal mutation database — for p53 (www.p53.free.fr/).[3] The distribution of the loss-of-activity *TP53* mutant is out of range as compared with previous studies of breast carcinoma ($P<0.001$).[4] Overall, the pattern of p53 mutations described in this study is consistent with either technical problems — commonly encountered with the use of paraffin-embedded tissue — or a mutator phenotype associated with random passenger mutations.

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TO THE EDITOR: Among 32 specimens from patients with hereditary breast cancer with *TP53* mutations, Patocs et al. reported that 11 specimens had mutations in stroma alone and 10 had mutations in both epithelium and stroma. Fourteen of these 32 mutations predicted Pro89Ser, of which 5 were simultaneously encountered in epithelium and stroma, arguing for a common genetic lineage. Pro89Ser is an infrequent mutation that appeared only twice in the universal mutation database for p53[1] and three times among the 24,810 mutations compiled in the International Agency for Research on Cancer p53 database.[2,3] This mutation is predicted to be neutral for its effects on p53 protein structure.[4] The mutant protein is able to transactivate eight different p53-dependent promoters in yeast functional assay. Therefore, the role of Pro89Ser as a loss-of-function mutation in carcinogenesis appears to be questionable. Indeed, in the study by Patocs et al., such a mutation was not found among the 74 *TP53* mutations in the group of patients with sporadic breast cancer. We feel that the absence of an association of stromal *TP53* mutations with a positive nodal status in hereditary breast cancer could be the consequence of the inclusion of such a mutation in the statistical analysis.

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TO THE EDITOR: The study by Patocs et al. cannot exclude biases regarding hereditary breast cancer. The number of patients with *BRCA1* mutations (25 patients) or *BRCA2* mutations (16 patients) was small, and the authors included these two distinctly different groups[1,2] within the same heterogeneous group.

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THE AUTHORS REPLY: In their study, which they concede was underpowered, Campbell et al. were unable to find *TP53* mutations in 10 frozen "stroma" samples near breast-cancer epithelium, and they did not detect *TP53* mutations in the epithelium. The latter result suggests a systematic error, since 10 samples should yield one or more somatic *TP53* mutations in carcinomatous epithelium. A challenge of working with archival or frozen templates is to avoid artifacts. Although we selected intratumoral stromal fibroblasts, it is unclear whether Campbell et al. did actually obtain intratumoral stroma or normal stroma near the tumor. This group previously reported no genomic alterations or mutations in CD10-positive stroma, but in fact they had selected only for myoepithelial cells and rare intratumoral myofibroblasts.[1] When we used this selection, we also did not find genomic alterations or mutations from either archival or frozen template–derived DNA. Furthermore, almost all our germ-line DNA samples were also procured from archived templates of normal breast epithelium and normal stroma distinct from tumor after laser-capture microdissection (see Table 1 of the Supplementary Appendix, available with the full text of this letter at www.nejm.org). We always perform a series of quality-control measures for each study (see Table 1 of the Supplementary Appendix), as we report in our article. Finding the association between stromal *TP53* mutation status and lymph-node status would be extremely unlikely if the mutations were obtained by artifact. In addition, we found that in the absence of a *TP53* mutation, the loss of heterozygosity at five loci in stroma was associated with a positive lymph-node status. Genes that encode proteins in the p53 pathway lie in three of these five loci, again corroborating the biology behind our data.

With regard to the comments by Zander and Soussi and by Zalcman et al., comparisons of somatic *TP53* mutational spectra from databases with our compartment-specific spectra are comparisons of apples with oranges. Existing databases register somatic mutations derived from analyses of variable numbers of exons from whole breast tumors (a variable admixture of epithelium, stroma, and germ-line cells), using mutation-detection techniques of variable sensitivities. Thus, no rigorous conclusions can be drawn from these databases.

Finally, with regard to the comments of Roukos, we suspect that intratumoral stromal genetic alterations might be found in other tumors. Stromal genetic alterations and mutations have been independently described in carcinomas of the head and neck, colon, bladder, and cervix and in inflammatory bowel disease.[2-4]

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