**THE AUTHORS REPLY:** Josephson highlights the fact that some lawsuits might name several physicians, and many of these physicians will ultimately be dropped from the suit. Thus, although less than one fourth of physicians facing a malpractice claim make a payment to a patient, it is possible that more than one fourth of patients seeking compensation receive it.

Our estimated risks are not intended, however, to describe the likelihood that a malpractice lawsuit will result in payment, but rather that a physician against whom a claim is filed will make a payment (through his or her insurer). This latter percentage, which is what we calculated in our article, is probably more important to understanding perceptions of malpractice among physicians. Although the percentage of lawsuits resulting in patient compensation is important for understanding the incentives of patients to pursue malpractice claims, our data did not allow us to estimate this percentage, since not all physicians involved in a case are necessarily covered by the insurer we studied.

DeVille et al. arouse concern that our definition of malpractice risk may be too broad and that the risk of suits against physicians is lower than what we estimated. They are correct to note that many claims against physicians do not result in suits, and we had anticipated this concern when we wrote our article. In our analysis, we eliminated all claims in our data that had no associated defense costs, which should make up the majority of the nuisance claims that they allude to. Although claims that result in costly and lengthy litigation against physicians probably contribute most to perceptions of malpractice risk among physicians, claims that do not reach the status of a formal lawsuit are also likely to affect these perceptions. Our focus on claims with positive defense costs thus conservatively estimates malpractice risk from a physician’s point of view.

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**HRAS Mutation Mosaicism Causing Urothelial Cancer and Epidermal Nevus**

**TO THE EDITOR:** Mosaicism of an oncogenic AKT1 mutation causes Proteus syndrome, which is associated with epidermal nevi and an increased risk of cancer. The occurrence of oncogenic mutations in mosaicism may increase a person’s risk for malignant conditions. Somatic RAS mutations occur in 30% of tumors; germline mutations have been identified in rare developmental disorders, such as HRAS mutations in the Costello syndrome. Here we report on a patient with multiple urothelial tumors reflecting mosaicism of an oncogenic HRAS mutation.

A 49-year-old man presented with a widespread congenital epidermal nevus (Fig. 1). When he was 19 years of age, a stage TaG1 urothelial-cell carcinoma was detected in the bladder and was treated by means of transurethral resection. After a tumor-free interval of 29 years, two stage T1G3 urothelial-cell carcinomas were diagnosed in the bladder and renal pelvis. One year later, a single metastatic lesion developed in the lung. He had no other clinical features of the Costello syndrome. This patient also has an HIV-1 infection that has been stabilized with antiretroviral drug therapy.

An HRAS p.G12S mutation was detected in the epidermal nevus, the three urothelial-cell carcinomas, and the lung metastatic lesion, as well as in normal lung tissue, blood leukocytes, and non-neoplastic urothelium (Fig. 1). However, it was undetectable in DNA from the bladder-muscle layer and two cutaneous angiomas. These results provide evidence of an embryonic HRAS p.G12S mosaic mutation affecting tissues derived from
endoderm (urothelium), ectoderm (skin), and mesoderm (blood) and contributing to the development of multiple urothelial-cell carcinomas in adults. All these carcinomas lacked mutations in FGFR3, PIK3CA, TP53, and PTEN. Array-based comparative genomic hybridization analysis revealed congruent aberrations in the urothelial carcinoma of the renal pelvis and in the lung metastatic lesion, supporting their genetic relatedness.

This patient has a postzygotic mosaic HRAS mutation resulting in a widespread epidermal nevus and a predisposition to cancer. Although this phenotype differs from that of patients with the classic Costello syndrome, mosaicism in this syndrome has been described. Phenotypes may vary because of the different tissue compartments affected by the mosaic mutation.

Thus, some HRAS mutations detected in adult solid tumors may have already occurred during embryogenesis. Tumors that arise in young patients without familial cancer and in those who present with lesions that are multicentric or evident in multiple organs may result from congenital postzygotic mutations. Furthermore, HRAS mosaic mutations may contribute to non-neoplastic diseases and to the pleiotropy of disease phenotypes. If we consider that approximately 0.1% of the population harbors an epidermal nevus at birth, and that similar congenital lesions in internal tissues may go unnoticed, em-
bryonic oncogenic mosaic mutations in adult cancers may be more common than has previously been thought.

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TO THE EDITOR: Exposure to high altitude elicits integrated physiological responses to permit survival during hypoxia. Natives of Tibet living at high altitude have adapted in part through the generation of high levels of nitric oxide and circulating nitrogen oxide species that enable greater blood flow and oxygen delivery to offset hypoxia.1 Therefore, we hypothesized that in lowlanders acclimatizing to high altitude, levels of circulating vasoactive nitrogen oxides would increase to counteract hypoxia. To test this hypothesis, we assessed levels of extracellular and erythrocytic nitrogen oxide species in 15 persons living in low-altitude areas as they ascended in altitude during a 19-day trek in Nepal (Fig. 1A).

Oxyhemoglobin saturation fell progressively during ascent (Fig. 1B), whereas arterial oxygen content decreased at 3440 m but did not decrease further at 5050 m because of the increase in hemoglobin content (Table 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). In a finding that is consistent with this phenomenon, the levels of two proteins regulated by hypoxia-inducible factor (HIF), endothelin-1 and erythropoietin, increased at high altitude (Fig. 1C, and Table 1 in the Supplementary Appendix).

Levels of serum, urinary, and salivary nitrate and nitrite increased in all participants at 3440 m (Fig. 1D through 1G). On further ascent, levels of salivary, urinary, and serum nitrate decreased while serum nitrite levels plateaued (Fig. 1D through 1G). In contrast, levels of intracellular red-cell forms of nitric oxide, S-nitrosohemoglobin and iron nitrosyl hemoglobin, which at 1300 m were similar to those reported elsewhere in healthy persons,2 increased strikingly during ascent to 5050 m (Fig. 1H and 1I). Although the fact that blood samples were collected in the field but assayed at sea level may have led to some degree of sample oxygenation that may have affected levels of S-nitrosohemoglobin, uniform handling of the samples permits a valid comparison of relative changes across samples.

To assess the effects of acclimatization on function, we used the 6-minute walk test. The average distance walked at peak altitude was 86% of the distance walked at baseline (P<0.001). With the use of stepwise regression, we identified the levels of S-nitrosohemoglobin, endothelin-1, and hemoglobin as making positive contributions to the distance walked in 6 minutes (R² = 0.81; P = 0.01).

Although the number of study participants was small, the results clearly identify nitrogen oxides as integral components in acclimatization to hypobaric hypoxia. The reaction of nitric oxide with hemoglobin greatly limits the lifetime of nitric oxide in blood; thus redox-activated nitrogen oxides, such as nitrite and S-nitrosothiols, have been proposed as enablers of hypoxia-associated vasodilation.3,4 In this context,