suggests the high interindividual variability in response. It is unclear what the underlying causes of such differences are. Can polymorphism of TLR and several other cytokine receptors as described in previous literature play a role?[3–5] It is unclear from the study how to modify these inflammatory responses to surgery from the perspective of an anesthesiologist. Investigation of different immunologic compounds in sepsis and other critical care grade of insults to the immune system failed to modify any outcomes. This is attributed at least partially to lack of sufficient fidelity in testing of the status of the immune system as well as lack of understanding how clinical interventions will affect incredibly convoluted and interdependent responses of the immune system to stress. Additionally, if polymorphism is to be blamed for the wide range of responses, our ability to affect these responses is very limited due to the underlying patient characteristics.

The stimulation used to activate samples of blood was lipopolysaccharide and several cytokines. Lipopolysaccharide should not be present in bloodstream during the elective "clean" surgery.[6–8] It is also worth mentioning that the primary mediators of the activation are intracellular danger signals like adenosine, low pH, heat-shock proteins, or high-mobility group box protein 1.[5] Some of these mediators share activation *via* TLR4/CD14 system, while some of them do not. Moreover, the concentration of lipopolysaccharide (1 μg/ml) was exceptionally high. At such concentration, activation of apoptosis is abundant, while other pathways mediated by lipopolysaccharide are less pronounced.[9] Similar remarks can be made with respect to cytokine cocktail used for stimulation. Therefore, it should be concluded that the stimulation mixture used in the study is artificial and may never be seen during elective surgery.

Finally, testing of several psychosomatic variables is highly dependent on the preexisting psychologic makeup of patients. One would presume that at least some of the patients had significant physical impairment, pain, and fatigue. In the discussion, the authors identified this problem as a potential shortcoming of the study, and I want to further emphasize its importance.

The study by Fragiadakis *et al.* is a valuable resource. In previous work, they analyzed several data pertaining to activation of the immune system in the aftermath of the surgery. This study is a valuable addition, but their conclusions have to be taken with a grain of salt, considering the "artificial" stimulation regimen, correlational nature of the study, and the lack of long-term outcome data.

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Competing Interests

The author declares no competing interests.

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In Reply:

We appreciate the opportunity to respond to Dr. Laudanski's critical commentary. The key result of our study suggests that signaling activity of the Toll-like receptor 4 (TLR4) in a presurgical whole blood sample predicts the speed at which patients regain function of their operated hip.[1] We agree with Dr. Laudanski that nuclear factor kappa-light-chain-enhancer of activated B cells is ubiquitous. However, our findings are related to specific signaling events downstream of TLR4, including mitogen activated protein kinase-activated protein kinase-2, cyclic adenosine monophophate response element-binding protein, and ribosomal protein S6, that occurred in a precisely phenotyped subset of monocytes.[1,2] The detected signaling patterns were highly specific with respect to pathway and cell type, which diverges from Dr. Laudanski's view that "activation of the immune system is often non-specific." Our findings further highlight the sentinel role of TLR4 in detecting tissue damage and mediating sterile inflammation and extend previous work by linking TLR4 activation patterns to patients' functional recovery.[3,4] Functional recovery is at the very core of current enhanced recovery after surgery protocols, and delays of weeks, as reported by us and others, matter greatly to patients and healthcare providers.[2,5,6] A blood test identifying patients at risk

for delayed functional recovery is an important step toward providing individualized, effective, cost-conscious, and high-value care in the context of the perioperative surgical home.[7] While we agree that the blood test used an external or "artificial" TLR4 ligand (lipopolysaccharide) that may not recapitulate biology as it unfolds during surgery, the use of lipopolysaccharide to activate a specific signaling pathway does not negate the predictive value of the test.

The scientific endeavor never stops, and interesting results will always trigger the next set of important questions. While our strong correlative findings provide a link to relevant biology, we agree that they do not prove cause and effect—and we never in our report suggested such a relationship. This is the next obvious question that we need to address. The prospect of validating TLR4 as a therapeutic target is exciting in light of preclinical studies, suggesting that preemptive dampening of TLR4 with a nontoxic agonist attenuated proinflammatory events and enhanced host resistance to infection and survival in models of burn injury and systemic infection.[8,9]

There is certainly important work ahead of us and room to improve on all fronts. However, our bets have been placed, and we see a clear light at the end of the tunnel.

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Competing Interests

Dr. Nolan has a personal financial interest in Fluidigm (South San Francisco, California), the manufacturer of the mass cytometer used in this article. The other authors declare no competing interests.

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Ultrasonographic Appearance of the Cricothyroid Membrane

To the Editor:

We read with great interest the important article by Siddiqui *et al.*[1] published in the November issue of Anesthesiology, demonstrating that the use of ultrasound guidance may improve the cricothyrotomy success rate in cadavers with difficult landmarks. We also read with great attention the nice Editorial View by Asai,[2] which accompanies this article. One image (from J. P. Rathmell) in the center of the first page of this Editorial illustrates these two articles. Unfortunately, this picture does not seem to be an image of the cricothyroid membrane but, as much as we can see, an ultrasound image of the hyoid bone, represented "as an inverted U hyperechoic curvilinear line" as described by