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*A tipping point in cancer-immune dynamics leads to divergent immunotherapy responses and hampers biomarker discovery*

Predicting the effects of immunotherapy treatments on cancer patients remains a challenge. Efforts to overcome these challenges focus mainly on the discovery of new biomarkers. Owing to the complexity of cancers and their tumor microenvironment, only a limited number of candidate biomarkers eventually enters clinical practice, despite advances in cellular and molecular approaches. We used an ordinary differential equation model to simulate the fundamental mechanisms that dictate tumor-immune dynamics and investigated its implications on responses to immune checkpoint inhibition (ICI) and patient survival. By simulation of biomarker discovery trials, we extracted fundamental principles underlying the success rates of biomarker discovery programs. Our model predicts a tipping point – a sharp state transition between immune control and immune evasion – that induces a strongly non-linear relationship between patient survival and both immunological and tumor-related parameters. In patients close to the tipping point, ICI therapy may lead to long-lasting survival benefits, whereas patients far from the tipping point may fail to benefit from these potent treatments. Our findings imply that (1) the apparent conundrum that ICI induces substantial benefits in some patients yet completely fails in others could be, to a large extent, explained by the presence of a tipping point; (2) predictive biomarkers for immunotherapy should ideally combine both immunological and tumor-related markers, as the distance of a patient's status from the tipping point cannot be reliably determined from solely one of these. The notion of a tipping point in cancer-immune dynamics could help to optimize strategies in biomarker discovery.