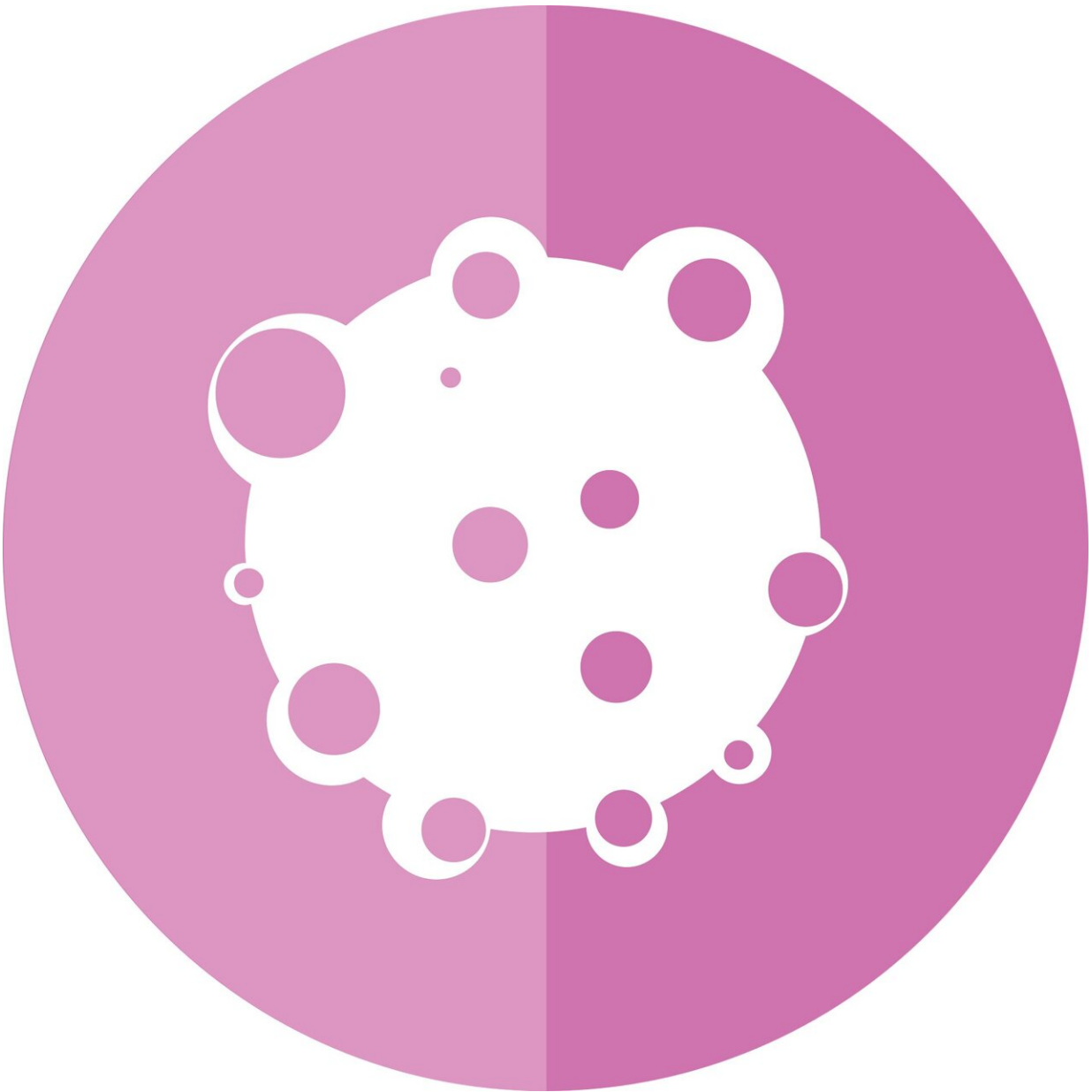


Study discovers that tumor mutation burden predicts survival outcome

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The expected course of a patient's cancer prognosis has traditionally been judged by its type, stage and microscopic aggressiveness, but patients with the same presentation can still have widely divergent outcomes. Researchers from Vanderbilt-Ingram Cancer Center have discovered that differences in tumor mutation burden are a major reason for this divergence.

The study, published in *JCO Precision Oncology*, has revealed that mutation burden is a fundamental predictor of survival, independent of the clinical presentation metrics currently used. The researchers state in the study that mutational indices can be "used to predict disease course as effectively as ([cancer](#)) stage or grade."

"A major insight of the study was the observation that survival was better at both low and high extremes of [tumor](#) mutation burden," said the study's corresponding author, William Dupont, Ph.D., professor of Biostatistics, Health Policy, and Preventive Medicine at Vanderbilt University Medical Center.

The study investigated the Pan-Cancer Atlas of 10,652 patients and 32 cancer types. Prior investigations had generally either tested models that made the unfounded assumption of a linear relationship—that survivability decreased with mutation burden—or that divided patients into low and high mutation burden groups for comparison. However, the researchers took a different analytic approach and found that survival is worse in the mid-range of mutation burden.

Under modeling that instead accurately fit the observed data, the relationship between mutation burden and survival proved to be

remarkably significant and clearly distinguished the survival outcomes even between two patients sharing cancer type, stage and grade.

"As a pathologist it is gratifying to see that the prognostic power of the microscope is enhanced by the genetic analysis of the cancer," said study author Fritz Parl, MD, Ph.D., recently retired professor of Pathology, Microbiology, and Immunology. "The types of tumor [mutations](#) that proved to be predictive included pathogenic substitutions and insertion-deletions, as well as copy number alterations."

A high tumor mutation burden is currently an indication approved by the Food and Drug Administration for the use of immunotherapies. In that context, the measure reflects neo-antigen load, or how foreign a tumor would appear to a patient's own immune system. However, data from the Pan-Cancer Atlas predates immunotherapies, so this treatment advancement is not a factor for the longer survival by patients with high tumor mutation burdens.

"The discovery reveals that measure of tumor mutation burden could have a far broader indication: stratifying patients at the time of initial treatment decisions—analogously to the traditional use of stage and grade," said study author Jeffrey Smith, MD, Ph.D., associate professor of Medicine.

The study discovered that genome mutation burden is a fundamental determinant of cancer outcome. The authors provide a web-based application that clinicians and researchers can utilize for decisions in clinical trial design and patient care.

More information: Jeffrey R. Smith et al, Mutation Burden Independently Predicts Survival in the Pan-Cancer Atlas, *JCO Precision Oncology* (2023). [DOI: 10.1200/PO.22.00571](https://doi.org/10.1200/PO.22.00571)

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