Precision oncology insights revealed for colorectal cancer

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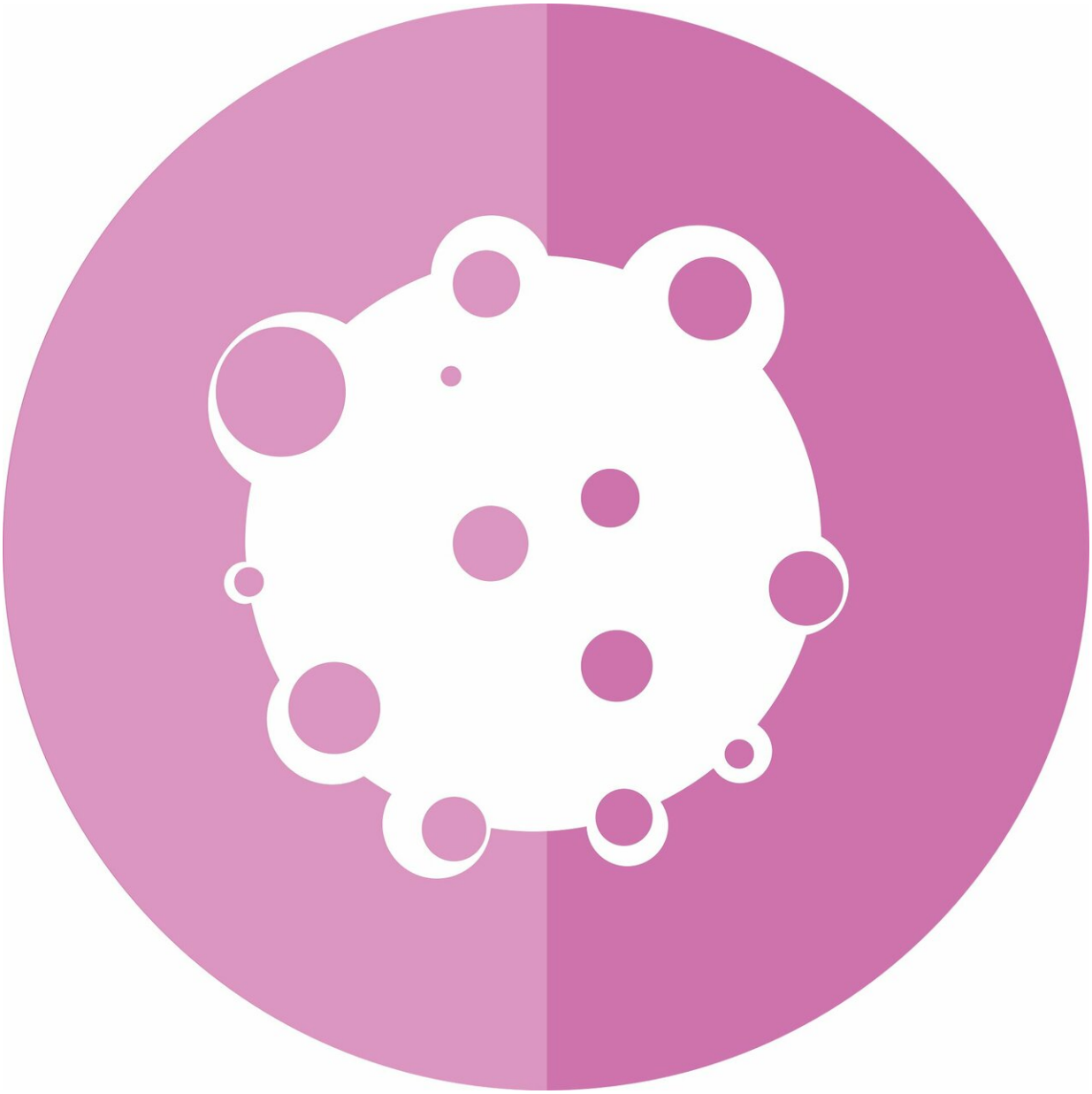

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Next-generation sequencing of tumor DNA from patients with colorectal cancer revealed genetic alterations that were linked to different survival and treatment outcomes in an analysis led by a University of North Carolina Lineberger Comprehensive Cancer Center researcher.

The findings, published in the *Journal of Clinical Oncology*, could help define strategies to more effectively treat colorectal cancer, the second leading cause of cancer death in the United States.

"This is an example of precision oncology, where using genetics, we are able to stratify tumor types that we once believed were homogeneous, and to identify new patient subgroups that might benefit from tailored therapies," said UNC Lineberger's Federico Innocenti, MD, Ph.D., associate professor in the UNC Eshelman School of Pharmacy Division of Pharmacotherapy and Experimental Therapeutics.

For the study, researchers analyzed mutations in tumors of 843 patients who participated in a phase III clinical trial. The trial compared treatment with chemotherapy plus either bevacizumab or cetuximab—regimens which are now the standard of care for this disease in the advanced stage. The researchers used tumor samples to analyze genetic mutations in the DNA. Then, they examined associations between the mutations and data on patients' responses to the treatments and survival.

One key finding from the analysis was that patients who had a lot of genetic repeats in their tumor DNA—known as microsatellite instability—had longer survival when treated with bevacizumab compared to patients treated with cetuximab.

"This finding has important potential implications for treatment of patients with microsatellite instability—a subgroup that represented about 7 percent of patients in our study," Innocenti said.

Another key finding was that patients with tumors that had more genetic variation, which they called high tumor mutational burden, lived longer than patients who had tumors with less variation. The level of tumor mutational burden defines a new subgroup of patients with better prognosis, Innocenti reported.

Studies are ongoing in Innocenti's lab to try to understand the role of the body's immune system in contributing to the finding. Researchers want to know if these patients with higher tumor mutational burden will be more responsive to treatments that work by unlocking the immune system against cancer.

"It is crucial to define which patients could be responsive to immunotherapy in this setting, and this study shows the first promising evidence to do so," Innocenti said.

The study also confirmed findings previously made for patients who had mutations in the BRAF gene in their tumors. They found these patients had worse survival compared to patients who didn't. Median survival for patients with the mutation was 13.5 months, compared to 30.6 months in patients without mutations.

"This mutation was a very strong negative prognostic factor," Innocenti said. "There was a clear difference in survival."

There was no difference in the study between the different treatment strategies studied in the trial for patients with or without the BRAF mutation. However, Innocenti said the finding confirms these tumors have a different biology and should be treated differently.

Additional studies are needed to evaluate and confirm findings with therapeutic implications in patients, Innocenti said. Further research is planned to study additional ways of stratifying patients based on their genetic features to improve outcomes.

More information: Federico Innocenti et al. Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome, *Journal of Clinical Oncology* (2019). DOI: 10.1200/JCO.18.01798

Provided by UNC Lineberger Comprehensive Cancer Center

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