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Mutations in DNA damage repair genes associated with response to cisplatin in bladder cancer

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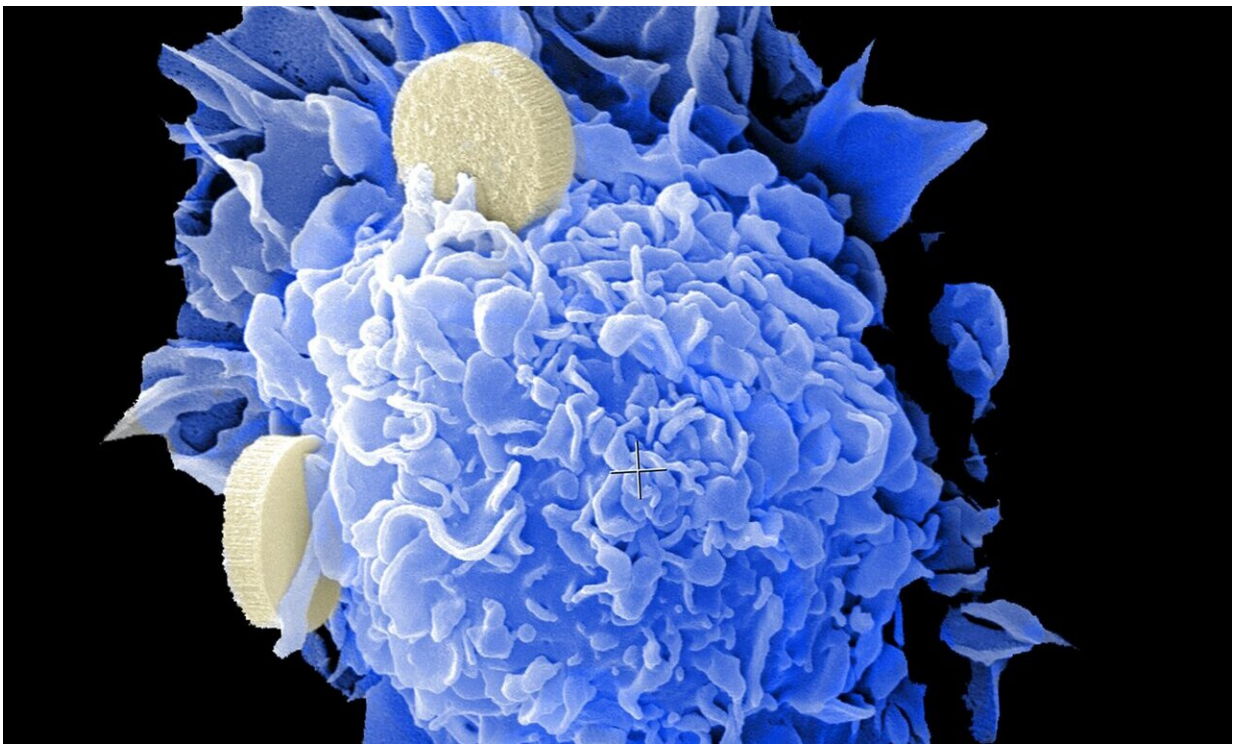

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An analysis of pre-treatment tumor specimens from 105 patients with localized muscle-invasive bladder cancer found that the presence of a mutation in any one of three genes, all known to be involved in DNA

damage repair, was associated with complete pathologic response to cisplatin-based neoadjuvant chemotherapy as measured by pathological downstaging at the time of bladder surgery. Results are published in the journal *European Urology*.

"The SWOG S8710 randomized trial provided Level 1 evidence supporting the use of neoadjuvant chemotherapy in eligible patients with muscle-invasive bladder cancer, but uptake was disappointing because the magnitude of the effect was considered modest," said David James McConkey, Ph.D., of Johns Hopkins Greenberg Bladder Cancer Institute, senior author on the article.

"So we designed the S1314 COXEN trial to test whether a tumor biomarker known as the COXEN score could predict which patients had tumors that were likely to respond to neoadjuvant chemotherapy." Primary results of S1314 were published in *Clinical Cancer Research* in 2021.

The new analysis used banked tissue samples from S1314 patients to test the complementary hypothesis that mutations in specific DNA damage repair genes were enriched in tumors that were sensitive to the drug cisplatin, and therefore tumors with these mutations were more likely to be eradicated (completely cleared) by cisplatin-based neoadjuvant chemotherapy.

Results of the analysis support this hypothesis. Patients whose tumors had a mutation in the ERCC2, ATM, or RB1 gene were more than five times as likely (compared to patients whose tumors lacked such mutations) to achieve a complete pathologic response to the chemotherapy, meaning that their tumors had disappeared by the time of surgery.

The authors suggest that a pre-treatment test for mutations in these three

genes, when combined with careful clinical assessment, might be helpful in determining which patients can be considered for continued surveillance instead of bladder surgery. The RETAIN trial and other similar studies are now collecting data to test this hypothesis.

"The evolution of more effective systemic neoadjuvant therapies in conjunction with innovative tools such as urine-based tests for detection and monitoring patients on bladder surveillance will build on this work toward a goal of avoiding cystectomy in cases where radical surgery is not required to achieve cure," said Elizabeth R. Plimack, MD, MS, FASCO, of Fox Chase Cancer Center, lead author of the new work.

More information: Elizabeth R. Plimack et al, Correlative Analysis of ATM, RB1, ERCC2, and FANCC Mutations and Pathologic Complete Response After Neoadjuvant Chemotherapy in Patients with Muscle-invasive Bladder Cancer: Results from the SWOG S1314 Trial, *European Urology* (2024). DOI: 10.1016/j.eururo.2024.06.018

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