# Some cases of Lynch syndrome are missed in younger patients under current screening guidelines: study

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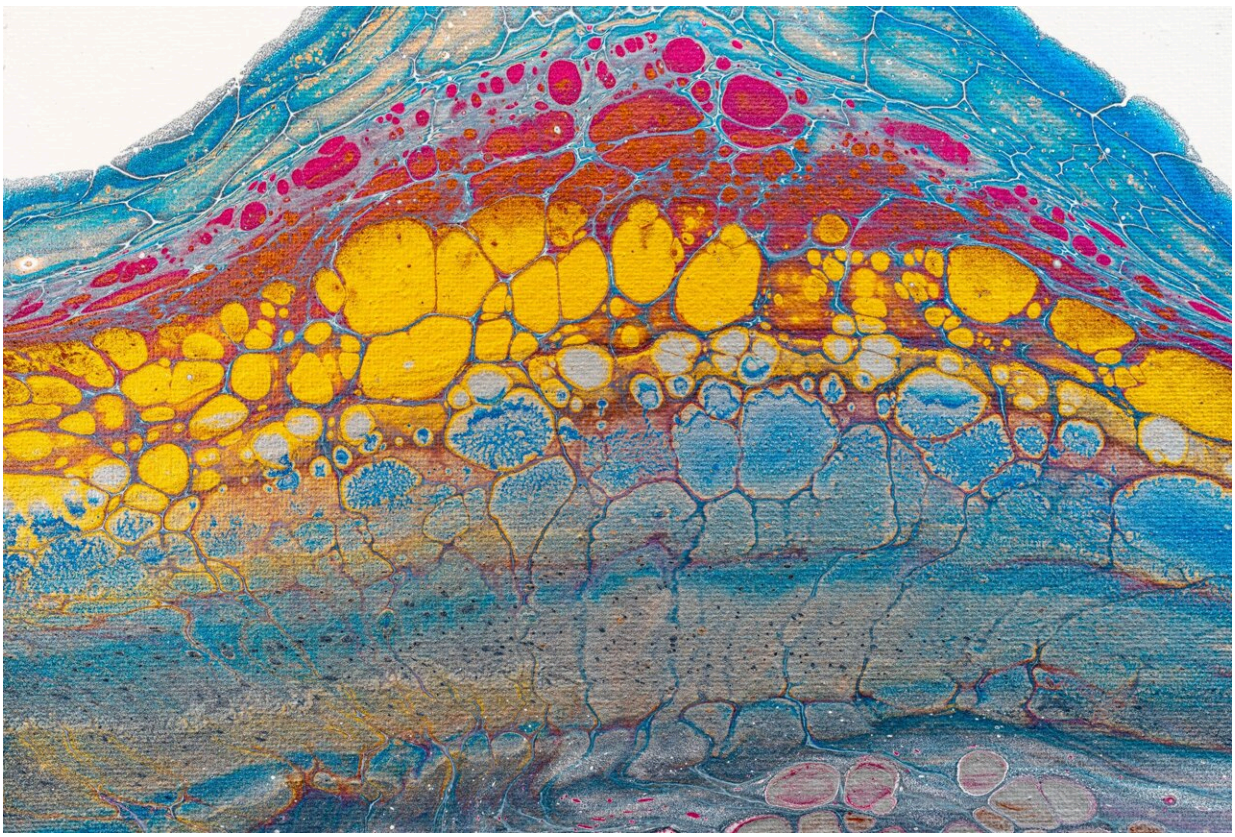

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New research from Cedars-Sinai Cancer investigators could warrant reconsideration of current screening guidelines to include a poorly

recognized cause of Lynch syndrome, the most common cause of hereditary colorectal and endometrial cancers. Their study, published today in the *JNCCN—Journal of the National Comprehensive Cancer Network*, concluded that the guidelines leave a significant number of patients undiagnosed.

"When patients with Lynch syndrome—whose first cancers generally appear at an early age—aren't diagnosed promptly, they don't get appropriate follow-up or surveillance," said Megan Hitchins, Ph.D., director of Translational Genomics in the Department of Biomedical Sciences at Cedars-Sinai and lead author of the study. "They can go on to have multiple different cancers before they are finally diagnosed. If we could identify them when they have their first cancer, we could prevent additional cancers—or at least detect them earlier."

Many colorectal and endometrial cancers have something called mismatch repair deficiency. This means that the tumor formed because of mistakes that occurred when DNA was copied during cell division.

In most cases of Lynch syndrome, this mismatch repair deficiency is caused by an inherited mutation in a DNA mismatch repair gene. But mismatch repair deficiency can also be caused by something called methylation. This is a change to a gene called MLH1.

"Methylation isn't hard-wired into the gene the way a mutation is," said Hitchins. "It's added on, like debris clogging an engine. The engine itself is not defective, but it doesn't work properly because it's been clogged."

*MLH1* methylation is present in as many as 75% of tumors with mismatch repair deficiency, Hitchins said. It is usually present only in the tumor, meaning the defect is not inherited and the patient does not have Lynch syndrome.

"However, our study found that in a small fraction of patients, the methylation *is* present in normal tissues. It isn't confined to the tumor. This predisposes cells to cancer development," Hitchins said. "Because methylation is usually only present in the tumor, these patients have been automatically identified as non-Lynch patients, and never given the blood testing that would diagnose them with Lynch syndrome."

To help determine how often this takes place, investigators reviewed data from two large retrospective population-based studies, and tested blood DNA from all mismatch repair deficient colorectal cancer patients who participated. Among patients age 55 and younger who had methylation in their tumors, 25%-75% also had methylation in their blood, meaning they had Lynch syndrome but had not been diagnosed.

In a previous study published in the journal *Gynecologic Oncology,* Hitchins and fellow investigators tested the blood of patients with endometrial cancer from the same patient populations. They found that approximately 30% of endometrial cancer patients had methylation in their tumors. And among those under age 50, 15%-20% also had methylation in their blood, indicating Lynch syndrome, Hitchins said.

"Taken together, these studies suggest this population of patients would benefit from a change in screening guidelines," said Dan Theodorescu, MD, Ph.D., director of Cedars-Sinai Cancer and the PHASE ONE Distinguished Chair. "Appropriate screening can provide the opportunity for potentially lifesaving surveillance and early detection and treatment of subsequent cancers."

For now, Hitchins recommends that colorectal cancer patients under age 56 and endometrial cancer patients under age 50 ask their healthcare providers about additional screening for themselves—and their parents, siblings and adult children. She also suggested that primary care providers and oncologists reach out to young patients from the past five

years whose endometrial or colorectal tumors tested positive for MLH1 methylation.

"We've been finding young patients with endometrial or colorectal cancer who are told they don't have Lynch syndrome, then go on to develop a colon or other cancer that might have been prevented, or at least detected earlier," Hitchins said. "Those patients are walking around oblivious to their risk, and should be made aware of that fact and given the option of having a test."

**More information:** Megan P. Hitchins et al, Constitutional MLH1 Methylation Is a Major Contributor to Mismatch Repair–Deficient, MLH1-Methylated Colorectal Cancer in Patients Aged 55 Years and Younger, *Journal of the National Comprehensive Cancer Network* (2023). DOI: 10.6004/jnccn.2023.7020

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