Study identifies strategy for improved screening for type of hereditary colorectal cancer

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In a comparison of strategies to identify individuals with Lynch syndrome, the most common form of hereditary colorectal cancer (CRC), caused by mutations in certain genes (DNA mismatch repair [MMR] genes), universal tumor MMR testing among certain CRC patients had a greater sensitivity for the identification of Lynch syndrome compared with multiple alternative strategies, although the diagnostic improvement was modest, according to a study in the October 17 issue of *JAMA*.

Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer-related death. "Identification of patients with Lynch syndrome needs to be improved because, unless there is strong clinical suspicion, the majority of cases remain undetected, leading to the lack of implementation of highly effective preventive measures. Indeed, intensive CRC screening by colonoscopy and prophylactic gynecological surgery have been demonstrated to reduce both the incidence and mortality of these tumors," according to background information in the article. Tumor MMR testing is the cornerstone for identification of Lynch syndrome. "However, it is still under debate which CRC patients should undergo these analyses."

Leticia Moreira, M.D., of the University of Barcelona, Spain, and colleagues conducted a study to determine a highly sensitive and efficient strategy for the identification of MMR gene mutation carriers

among CRC probands (first identified individuals affected with the disorder among other family members). The study consisted of a pooled-data analysis of 4 large groups of newly diagnosed CRC probands recruited between 1994 and 2010 (n = 10,206) from the Colon Cancer Family Registry, the EPICOLON project, the Ohio State University, and the University of Helsinki. The researchers examined personal and family characteristics as well as other tumor and genetic factors and characteristics. Performance characteristics of selected screening strategies (Bethesda guidelines, Jerusalem recommendations, and those derived from analysis of variables associated with Lynch syndrome) were compared with tumor MMR testing of all CRC patients (universal screening).

Of 10,206 unrelated CRC probands, 312 (3.1 percent) were MMR gene mutation carriers. The researchers found that universal tumor testing (sensitivity, 100 percent; specificity, 93.0 percent; diagnostic yield, 2.2 percent) was superior to the selective strategy (sensitivity, 95.1 percent; specificity, 95.5 percent; diagnostic yield, 2.1 percent), Bethesda guidelines (sensitivity, 87.8 percent; specificity, 97.5 percent; diagnostic yield, 2.0 percent), and Jerusalem recommendations (sensitivity, 85.4 percent; specificity, 96.7 percent; diagnostic yield, 1.9 percent). "However, differences in diagnostic yield from the universal approach were small, with a difference between universal screening and the next less intensive strategy (i.e., selective strategy) of only 0.11 percent and accompanied by an increase in false-positive yield of 2.5 percent. Indeed, the selective strategy resulted in a 34.8 percent fewer CRC patients requiring tumor MMR testing and an additional 28.6 percent fewer cases undergoing germline MMR mutational analysis in comparison with universal screening."

"Results of this international, multi-center, pooled-data analysis demonstrate that unless a universal screening approach consisting of tumor MMR testing in all CRC patients is performed, a clinically

meaningful proportion of MMR gene mutation carriers will remain undiagnosed. Specifically, use of the revised Bethesda guidelines will miss approximately 12 percent, use of the Jerusalem recommendations will miss approximately 15 percent, and use of a selective criteria [performing tumor MMR testing of CRC probands diagnosed at 70 years or younger or fulfilling 1 or greater criterion of the revised Bethesda guidelines] will miss approximately 5 percent," the authors write. "These data may be useful to more empirically inform discussions on the most efficient approaches for the identification of Lynch syndrome among CRC probands."

"Universal tumor screening has, as expected, the highest sensitivity. Although it is not sufficient to just consider sensitivity when comparing different strategies, this is the most important parameter clinically (i.e., to minimize the number of patients with undiagnosed Lynch syndrome). Indeed, it is accepted that the whole Lynch syndrome screening process is cost-effective when the benefits to immediate relatives of identified patients are considered; accordingly, the more patients who are diagnosed, the more at-risk relatives can undergo genetic evaluation and receive appropriate cancer surveillance and other preventive interventions."

In an accompanying editorial, Uri Ladabaum, M.D., M.S., and James M. Ford, M.D., of the Stanford University School of Medicine, Stanford, Calif., write that "the potential for individualized preventive medicine provides the rationale for screening for Lynch syndrome."

"In deciding whether to establish widespread screening for Lynch syndrome in selected subgroups, the same considerations that govern screening for CRC in the general population could be applied. The target condition must be common enough to justify screening. A long asymptomatic period must allow for effective interventions. The potential benefits must outweigh the risks. The aggregate costs of

screening and its consequences must be acceptable."

More information: *JAMA*. 2012;308[15]:1555-1565
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