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Hereditary Syndrome Risk Assessment in all Colorectal Cancer Patients: Keep it Simple!

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STRUCTURED ABSTRACT

Question: How effective is universal mismatch repair deficiency (dMMR) testing of Colorectal Cancers (CRCs) in diagnosing patients with hereditary cancer syndromes?

Design: Prospective multi-center cohort.

Setting: Patients were recruited from 51 Ohio hospitals in the Ohio Colorectal Cancer Prevention Initiative from January 2013 to December 2016.

Patients: Adults undergoing resection for primary colorectal adenocarcinoma were included. Those with insufficient tissue, non-adenocarcinoma histology, or a diagnosis made outside of the study period or outside of Ohio were excluded. Of the 3,310 participants included in the study, 52.4% were male, 89.3% were non-Hispanic white, 78.3% were diagnosed after age 50 and 38.5% had right-colon tumors.

Intervention: All patients underwent tumor-based screening for dMMR with microsatellite instability (MSI) or immunohistochemistry (IHC) for mismatch repair proteins at a centralized laboratory. Those with abnormal

tumor screening and those who met clinical criteria underwent multi-gene panel germline genetic testing with a minimum 25-gene panel. Clinical criteria included CRC diagnosed under age 50 years, a personal history of synchronous or metachronous CRC and/or endometrial cancer (EC), or a family history of a first-degree relative with CRC or EC.

Funding: This study was supported by a grant from Pelotonia and, in part, by Grant No. P30 CA016058, National Cancer Institute. Myriad Genetics Laboratories donated germline next-generation sequencing testing for selected mismatch repair-proficient patients.

Results: Of the 3,310 patients with colorectal adenocarcinoma, 525 (15.9%) had dMMR by either MSI or IHC testing. Of the entire cohort, 1,498 met criteria for germline genetic testing based on tumor screening or clinical criteria. Germline testing was completed in 1,462 patients. Of all patients tested, 248 pathogenic or likely pathogenic variants were found in 234 patients (7.1% of the entire cohort, 16.0% of those tested). The majority of variants (69.2%) were found in genes associated with a high risk of colorectal cancer, such as Lynch Syndrome or polyposis. 6.8% of variants were found in genes associated with a high risk for non-colorectal cancers, such as *BRCA1* and *BRCA2* (**Figure**). Only 145 of 234 patients with a hereditary cancer syndrome had abnormal tumor-based screening. There were 9 patients diagnosed with Lynch Syndrome who had normal tumor-based screening.

COMMENTARY

Why Is This Important?

Hereditary cancer syndromes, caused by a pathogenic variant in a cancer predisposition gene, significantly increase risk of multi-organ cancers. Diagnosis of these patients is of utmost importance because it can change cancer treatment (such as extended colectomy or immunotherapy for Lynch Syndrome patients) and provide the opportunity for future multi-organ cancer prevention in patients and their family members.[1]

The current standard of care is to perform tumor-based screening for mismatch repair deficiency (dMMR) in all CRC patients to determine which patients should get germline testing.[2] This requires an organized multi-disciplinary program wherein all CRC tumor samples undergo MSI or IHC testing and requires an infrastructure to interpret results and ensure patients

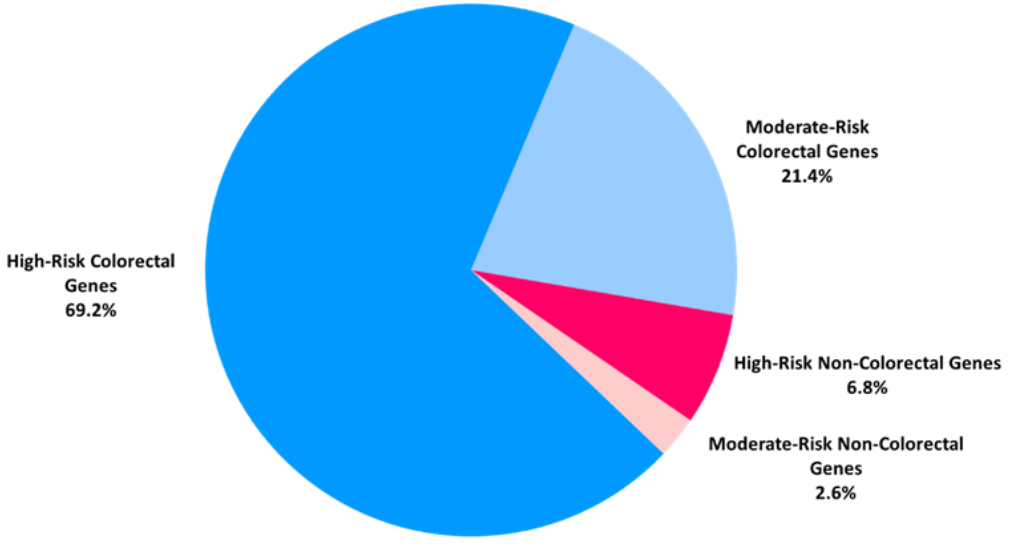

Figure 1. Spectrum of Pathogenic Variants found in Patients with CRC
High-Risk Colorectal genes included Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), Familial Adenomatous Polyposis (*APC*), *MUTYH* Associated Polyposis (biallelic *MUTYH*) and Juvenile Polyposis Syndrome (*BMPR1A*, *SMAD4*).
Moderate-Risk Colorectal genes included monoallelic *MUTYH, APC I1307K, CHEK2, ATM.*
High-Risk non-colorectal genes included *BRCA1*, *BRCA2, PALB2, CDKN2A, NTHL1, POT1*
Moderate-Risk non-colorectal genes included *BRIP1, NBN, GALNT12, RPS20*
For patients who had more than one pathogenic variant, the variant with higher risk and/or colorectal risk was counted.

are appropriately referred for germline testing. Even when implemented perfectly, this approach only screens for the most common hereditary CRC syndrome, Lynch Syndrome. There is minimal population-based data on the effectiveness of tumor-based screening for diagnosing hereditary cancer syndromes.

With the emergence of accessible and affordable multi-gene panel testing, where patients can get direct germline testing for all hereditary cancer syndromes, it is unclear if tumor-based screening should remain our standard of care or whether we should consider offering all CRC patients direct multi-gene panel germline testing.

Key Study Finding
This is the largest, and closest to population-based, cohort of CRC patients to undergo tumor-based screening. This study found that 7.1% of 3,310 unselected CRC patients have a hereditary cancer syndrome. 76% of syndromes are associated with a significantly increased risk of CRC (69%) or non-colorectal cancers (7%), where there are guideline-based

recommendations for more intensive screening, chemoprevention and even prophylactic risk-reduction surgeries. Identification of these syndromes would substantially change clinical management of patients and family members and has the potential to decrease cancer-related burden.

Unfortunately, the current standard of care of tumor-based screening for mismatch repair deficiency missed 38.6% of patients with a hereditary cancer syndrome, including 9 patients with Lynch Syndrome.

Caution

Because widespread multi-gene panel testing emerged in the midst of this study period and the extent of genes included on panels continually changes, genetic testing panels in this study included 25-66 cancer genes. Thus, the testing performed was not uniform.

My Practice

This study shows that even when tumor-based screening is perfectly implemented in a study setting, this approach misses almost 40% of patients with hereditary cancer syndromes. Based on this data, I recommend all CRC patients undergo hereditary risk assessment with 3 simple steps: (1) We should be thinking about a possible hereditary syndrome in all patients we diagnose with CRC, regardless of age at diagnosis, family history or tumor characteristics. (2) I recommend ensuring that our pathology colleagues are performing tumor-based screening for dMMR on our CRC biopsy specimens instead of waiting until resection, since surgical management can change based on presence of a hereditary syndrome. (3) Finally, I recommend all patients with CRC be referred to a genetic counselor who can interpret tumor-based testing, collect multi-generation cancer family history and review the indications, benefits and expected yield of multi-gene panel testing for all CRC patients.

For Future Research

If a universal germline testing strategy is ultimately supported based on studies like this, more research will need to be done to determine exactly which genes should be included on a panel and how best to ensure equitable access to genetic testing and appropriate follow up care for newly diagnosed patients and their family members.

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