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RESEARCH SUMMARY

Paired Tumor and Germline Testing for Lynch Syndrome: Increasing Clarity for Patients

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Our study, recently published in *Journal of Clinical Oncology* (JCO), demonstrates how paired tumor/germline testing can confirm or indicate a significantly reduced likelihood of a diagnosis of Lynch syndrome (LS) for the majority of patients with mismatch repair deficient* (MMRd) colorectal cancer (CRC) or endometrial cancer (EC).

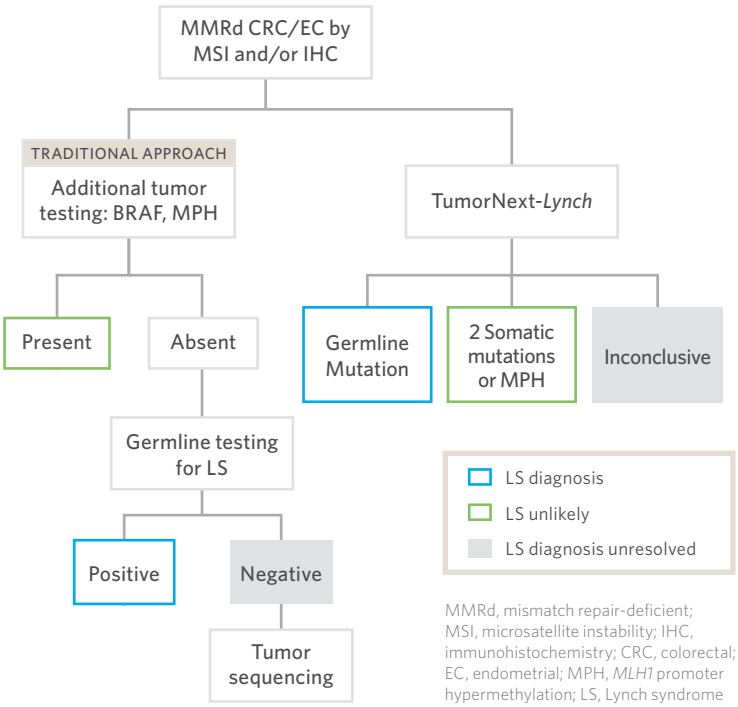
WHY THIS MATTERS TO YOU

Discordant results between tumor and germline testing for Lynch syndrome occur when the tumor screening results are suggestive of Lynch syndrome, but the germline results are normal. This situation can lead to uncertainty when recommending screening for patients and families. This study demonstrates that TumorNext-*Lynch* **provides clear answers for up to 76% of patients** with MMRd colorectal or endometrial tumors.

BACKGROUND

- Lynch syndrome (LS) is the most common inherited cancer predisposition syndrome accounting for 2-3% of CRC[1,2] and 2-3% of EC[3,4].
- LS results from a pathogenic germline mutation in *MLH1, MSH2, MSH6, PMS2* or *EPCAM*.
- Traditionally, screening for LS among newly-diagnosed CRCs and ECs has been a complicated process with multiple steps and the potential for an unclear diagnosis in patients with unexplained MMRd tumors (Figure 1).
- Biallelic somatic (tumor) mutations have been identified in 52-69% of unexplained MMRd tumors[5-7].
- This study evaluated the use of paired tumor/germline testing[8] to aid in the diagnosis of LS in >700 CRC and EC patients with MMRd tumors and/or clinical histories suggestive of LS.[9]

Figure 1. Diagnostic Workup for Lynch syndrome

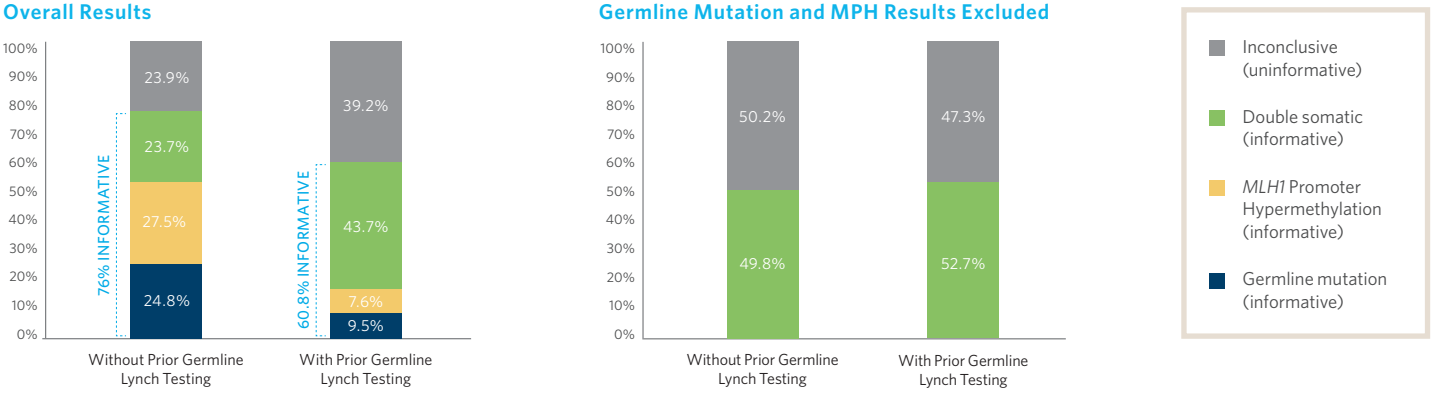


MMRd, mismatch repair-deficient; MSI, microsatellite instability; IHC, immunohistochemistry; CRC, colorectal; EC, endometrial; MPH, *MLH1* promoter hypermethylation; LS, Lynch syndrome

*MMRd = a tumor found to have loss of staining (aka abnormal IHC) for one or more of the mismatch repair proteins (MLH1, MSH2, MSH6, and/or PMS2) and/or a tumor with high micro-satellite instability (MSI-H). This evaluation is often done on newly diagnosed colorectal or endometrial cancers to screen for Lynch syndrome and determine eligibility for immunotherapy.

SIGNIFICANT FINDINGS[9]

Figure 2. TumorNext-*Lynch* Results for MMR-deficient Colorectal and Endometrial Cancer Cases



- TumorNext-*Lynch* was able to diagnose or indicate a significantly reduced likelihood of LS in **76.1% of cases without prior germline testing** and in **60.8% of cases with prior germline testing.**
- 24.8% of MMRd cases without prior germline testing were found to have LS.
- 9.5% of cases with **prior uninformative germline testing were diagnosed with LS.**
- A likely somatic explanation was found in **49.8% of cases that would have remained unresolved** without the addition of tumor sequencing analysis.

POINTS FOR YOUR PRACTICE

- In >75% of cases, TumorNext-*Lynch* provides clinicians and patients with a clear answer that can be used to guide risk counseling and medical management.
- Simultaneous tumor and germline analysis of the Lynch syndrome genes can provide more comprehensive information helping to avoid discordant results.
- TumorNext-*Lynch* offers a more streamlined approach to diagnose or rule out Lynch syndrome.

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