Background

Multi-gene testing is increasingly utilized in the clinical care of colorectal cancer (CRC) patients; however, the diagnostic yield and management implications of expanded panel testing are still emerging.

We retrospectively examined 107,068 patients referred for hereditary cancer syndrome genetic testing, of whom 35,350 had a personal history of CRC. Positive findings were compared in three categories: the initial clinician-specified genes, a 18-gene curated panel, and a large 75-gene multi-cancer panel.

Methods

1. All 35,350 patients with personal history of colorectal cancer, who had germline genetic testing of clinician-specified genes, were selected for this study from a larger cohort. Positive findings (i.e., pathogenic [P] or likely pathogenic [LP] variants in the clinical reports) were collected.

2. Under an IRB-approved research protocol, variants in additional genes included in the technical categories from a larger cohort.

3. Clinical diagnostic yield was compared between:
   a) the initially clinically genotyped patients, which vary by patient
   b) a fixed 18-gene panel of established CRC genes
   c) a 75-gene multi-cancer panel

* Computationally predicted LOD variants were stop gain, frame-shifting indels, or splice donor/acceptor site mutations.

Clinician Order: varied 1-75 cancer risk genes

18-gene simulated CRC panel:
- APC, AXIN2, BMPR1A, CDH1, CHEK2, EPCAM, GREM1, MSH1, MSH2, MSH6, MUTYH, PMS2, POLQ, POLQ, PTK2, SDHA, SDHB, SDHC, SDHD, SMAD4, SMCA1, SMCA2, SMAD5, SMAD6, STK11, TPS3, TP53, TSC2, VHL, WT2

75-gene simulate multi-cancer panel:
- ALK, APC, ATM, AXIN2, BAP1, BARO1, BMPR1A, BRCAL, BRCA2, BRIP, CASR, CCDC58, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CHEK2, CHK2, DFRS1, ESR1, EPCAM, FH, FLCN, GATA2, GPC3, GRIPE1, HAX1, KIAA1429, MKN, MEE, MET, MSH1, MSH2, MSH6, MUH, NF1, NF2, NF1, NF2, PAX2, PEG10, PHOSPH, PMS2, POLQ, POLQ, PTK2, PTEN, RAF1, RAD50, RAD51C, RAD51D, RET, RUNX1, SDHA, SDHB, SDHC, SDHD, SMAD4, SMCA1, SMCA2, SMAD5, STK11, SUFU, TERT, TERC, TMEM167, TP53, TSC1, TSC2, VHL, WT2

Results

What are clinicians ordering for CRC patients?

Lynch syndrome genes were requisitioned in 95% of all cases, and other established CRC genes in 85% of cases. Breast and ovarian cancer genes were requisitioned in approximately 55% of clinical orders, and 15% included other clinician-specified cancer risk genes.

Broadened the scope: Expanding ordering patterns in suspected hereditary CRC

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Approximately 90% of all P/LP findings were included in the initially requisitioned genes, and 18% of CRC patients were positive for one of these genes. Nevertheless, expanding the panel to 75 genes increased the yield by 11%, to a total of 20% of patients having a positive finding.

The 18-gene CRC panel had the lowest positive rate (15.8% of patients) reflecting the fact that clinician judgment in test ordering can increase diagnostic yield, although not as far as the 75-gene panel achieved.

Conclusions

Greater than 98% of all P/LP variants identified would be predicted to alter patient clinical care.

These data suggest that potentially actionable variants can be missed when adhering to restrictive test guidelines or using narrowly constructed disease-specific panels. It may be challenging for clinicians to select optimal sets of genes to test in each patient based on personal and family history. Clinicians may consider expanding the scope of their genetic tests in order to identify more at-risk patients and improve management of overall hereditary cancer risk. However trade-offs need to be considered as broad panels may increase VUS rates and uncertainty.