**Evaluation of the Outcomes of Tumor-Based Universal Screening for Lynch Syndrome in Patients with Colorectal Cancer in a Large, Diverse, Community-Based U.S. population**

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| Challenge | Lynch syndrome is the most common inherited colorectal cancer (CRC) syndrome, caused by pathogenic variants of mismatch repair (MMR) genes (*MLH1*, *MSH2*/*EPCAM*, *MSH6*, and *PMS2*). Patients with Lynch syndrome have lifetime risk of up to 80% for CRC and up to 60% for endometrial cancer, and lifetime risks for cancer of the prostate, stomach, ovaries, small intestine, hepatobiliary tract, urinary tract, and brain are also markedly elevated. Current professional society guidelines recommend screening all newly diagnosed CRCs for Lynch syndrome using immunohistochemistry (IHC) or microsatellite instability testing. However, successful implementation of the universal screening requires an effective collaboration of multiple specialties and can be practically challenging.  |
| Existing Evidence | Data regarding the real-world outcomes of universal screening remain very limited, particularly in the community-based setting. |
| Target Population | All KPNC patients diagnosed with CRC in 2011-2020 |
| Intervention or Exposure | Screening for Lynch syndrome using reflex tumor-based MMR IHC. BRAF V600E and/or MLH1 promoter methylation testing was considered for MLH1 deficient CRCs to exclude sporadic CRCs. |
| Outcomes/Key Findings | The study showed that successful implementation of tumor-based universal screening for LS using MMR IHC resulted in a substantial increase in the screening rate of over 10 years.Between 2011-2020, 8,744 patients with CRC were screened for Lynch syndrome using MMR IHC of CRC tumors. The percentages of CRCs with normal MMR IHC, MLH1/PMS2 deficiency, MSH2/MSH6 deficiency, MLH1 deficiency only, MSH2 deficiency only, MSH6 deficiency only, and PMS2 deficiency only were 84.3%, 11.1%, 0.8%, 0.1%, 0.3%, 0.4%, and 0.9%, respectively. The percentage of CRC tumors screened increased from 22.2% in 2011 to 92.0% in 2020 for all CRCs and from 23.0% in 2011 to 93.3% in 2020 for invasive CRCs. The rate of germline testing increased from 2.4% in 2011 to 20.9% in 2020 for all CRCs. One-hundred and eighty-eight patients (2.2%) were diagnosed with Lynch syndrome by germline analysis. Seventy-nine (0.9%), 1062 (12.1%) and 701 (8.0%) were diagnosed with variant of uncertain significance, Lynch-like syndrome, and sporadic CRC with MLH1 deficiency, respectively.  |
| Resulting Action/Change | The findings, from the largest dataset of outcomes of universal screening in a diverse US population, will inform strategies to promote universal screening for Lynch syndrome nationwide.  |
| Implementation Tools | The percentage of screened CRCs among all CRCs can be used as a quality metric for local facility, pathology and Genetics department to increase the screening rate in the future.  |
| Implementation and follow-up measurements | The percentages of screening among all CRCs periodically for quality improvement.  |
| Reference(s) [Key Figure if applicable] |  |