Abstract Title
Completion Of Follow-up After Abnormal Screening Test For Lynch Syndrome: A Framework For Multi-Level Cancer Care Delivery

Presenting author: Y. Nancy You (MD Anderson Cancer Centre, USA)
Y. Nancy You (MD Anderson Cancer Centre, USA), Eduardo Vilar (MD Anderson Cancer Centre, USA), Maureen Mork (MD Anderson Cancer Centre, USA), Sarah Bannon (MD Anderson Cancer Centre, USA), Sameer Patel (MD Anderson Cancer Centre, USA), Michael Egger (MD Anderson Cancer Centre, USA), Ashley Holder (MD Anderson Cancer Centre, USA), George Chang (MD Anderson Cancer Centre, USA), Brian Bednarski (MD Anderson Cancer Centre, USA), Craig Messick (MD Anderson Cancer Centre, USA), Barry Feig (MD Anderson Cancer Centre, USA), John Skibber (MD Anderson Cancer Centre, USA), Patrick Lynch (MD Anderson Cancer Centre, USA), Benedito Rossi (Hospital de Barretos, Brazil), Miguel Rodriguez-Bigas (MD Anderson Cancer Centre, USA)

Introduction: The Institute of Medicine has identified significant failures during transitions in cancer care. One focus has been the transition from screening to diagnostic evaluation and/or treatment. Failure to follow-up an abnormal screening test limits the benefit of screening and impedes further care. Because Lynch Syndrome (LS) is the most common inherited predisposition syndrome for colorectal cancer (CRC), testing CRCs for DNA mismatch repair deficiency (dMMR) has been advocated as a method to screen for patients at risk for LS. Current studies have focused on increasing tumor MMR testing, but little is known about the rate of followup when tumor-based screening is suggestive of LS.

Methods: A prospective protocol of universal tumor-based screening for LS enrolled 2134 consecutive CRC patients who underwent surgical treatment during 2009-2014. Tumor dMMR status was defined by either PCR-based MSI testing with >30% of the markers showing allelic shift, and/or immunohistochemistry (IHC) with loss of expression in MLH1, MSH2, MSH6, or PMS2. The complete process of follow-up care for patients who were screened to have dMMR CRC was standardized (Figure), and incorporated genetic counseling at the point of care by counselors who were integrated into CRC clinics, and long-term care through a dedicated high-risk familial cancer clinic. Four transition points of care were analyzed for the proportion of patients completing each metric.(Table)

Results: The median age at CRC diagnosis was 61.7 years (interquartile range: 53.5, 70.9) and 931 (43.6%) were female. Tumor MMR testing to screen for LS was completed in 1597 (74.8%) patients, and identified 180 (11.3% of 1597) patients with dMMR CRC. Followup of the dMMR result in 106 cases with loss of MLH1 included MLH1 promoter hypermethylation and/or BRAF mutation testing in 97 (91.5%) cases. After excluding 70 patients with MLH1 promoter hypermethylation and/or BRAF mutation accounting for dMMR, the remaining 110 patients were presumed to have LS. Genetic counseling was completed in 102 (92.7%) patients. Subsequently, 88 (86.3%)

completed confirmatory germline MMR mutation testing and 79 (77.5%) have enrolled in the familial cancer clinic.

Conclusion: When tumor MMR testing is utilized to screen for CRC patients at risk for LS, follow-up of patients with dMMR CRC involves several critical transitions in care, from screening to counseling, confirmatory diagnosis, and life-long care for the proband and kindreds. The high rates of successful follow-up observed were facilitated by a standardized care process, integration of genetic counseling within cancer clinics, and the specialized familial cancer clinic infrastructure. Ensuring the completion of followup after suggestive tumor-based screening is critical for delivery high-quality patient centered care in LS.

Summary of confirmatory germline tests for LS

	MLH1	MSH2	MSH6	PMS2
Pathogenic	16	15	11	3
Variant of unknown significance	2	2	1	0
Uninformative negative	12	10	13	8

Transition points in the care process after screening identifies a patient with dMMR CRC			
1	Patients screened to have dMMR CRCs with loss of MLH1 should be tested for MLH1 promoter hypermethylation and/or BRAF mutation prior to germline testing.		
2	Patients screened to have dMMR CRC without evidence of (1) above should undergo specialized genetic counseling.		
3	Screened and counselled patients undergo confirmatory and diagnostic germline mutation testing for LS.		

4	Patients with LS or presumed LS enroll in the high-risk familial cancer clinic for long-term care.		