Paired Tumor/Germline Testing for Lynch Syndrome in Endometrial Cancers – A Comprehensive Testing Approach

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Objectives: National guidelines recommend that all newly diagnosed endometrial cancers be universally screened for Lynch syndrome using microsatellite instability (MSI) or immunohistochemistry (IHC) analysis. In the absence of *MLH1* promoter hypermethylation or an identifiable germline mismatch repair (MMR) mutation, individuals with abnormal MSI or IHC have been managed as though they have Lynch syndrome. Recent data have shown that somatic analysis of the MMR genes in endometrial cancers may rule out Lynch syndrome in most cases. This study aimed to describe a new testing model for Lynch syndrome, whereby tumor and germline analyses are run concurrently (i.e. Paired testing).

Methods: A retrospective analysis was performed on data from endometrial cancer cases with abnormal IHC who underwent paired tumor/germline Lynch syndrome testing. Results of sequencing and deletion/duplication analyses of the MMR genes and *EPCAM* (del/dup only) in both tumor and germline DNA were assessed. Additional test results, including *MLH1* promoter hypermethylation testing and microsatellite instability (MSI) analysis, were also evaluated when available.

Results: In total, 68 cases were included (Table). Fifty three cases (78%) were informative, including 27 (40%) with double somatic alterations, 15 (22%) with germline MMR mutations, 9 (13%) with *MLH1* promoter hypermethylation alone, and 2 (3%) with likely false positive IHC results (no somatic alterations were found and MSI was stable). Fifteen (22%) of the original 68 cases were uninformative and had either one somatic mutation (9%) or no alterations in the tumor (13%).

Conclusions: Paired testing of both tumor and germline DNA provided an explanation for the MMR deficient endometrial cancers in 78% of cases. In this cohort, 56% of cases would have remained unexplained without the somatic testing of the Lynch syndrome genes. Adding tumor gene analysis to the testing algorithm allows for potential exclusion of Lynch syndrome and reduces the likelihood of discordant results. Combining both tumor and germline analyses reduces the number of steps needed for Lynch syndrome testing, while also providing clinicians with more comprehensive answers, which can then be used to further tailor treatment and surveillance for each patient.

Table: Case Details and Results

	N	% Total
Total cases	68	100%
No previous germline testing	52	76%
Previous germline testing	16	24%
Meets Bethesda guidelines	9	13%
Meets Amsterdam criteria II	3	4%

Average age of cancer diagnosis in years	59	
Informative cases	53	78%
-Double somatic alterations	27	40%
-Germline mutation	15	22%
-*MLH1* promoter hypermethylation only	9	13%
-False positive IHC (no hits and MSS)	2	3%
Uninformative cases	15	22%
-One somatic mutation	6	9%
-No somatic or germline alterations	9	13%