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

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BACKGROUND

- Appropriate candidates for Lynch syndrome genetic testing are often identified by abnormal microsatellite instability (MSI) and/or mismatch repair (MMR) protein immunohistochemistry (IHC) on colorectal and endometrial tumors.
- In the absence of a *BRAF* mutation, *MLH1* promoter hypermethylation, or an identifiable germline mutation, individuals with abnormal MSI and/or IHC are often managed as if they have Lynch syndrome.
- Recent data have shown that analyses of tumor DNA may exclude Lynch syndrome in many of these patients.
- This study aimed to describe the results of paired tumor/germline testing for Lynch syndrome at one laboratory.

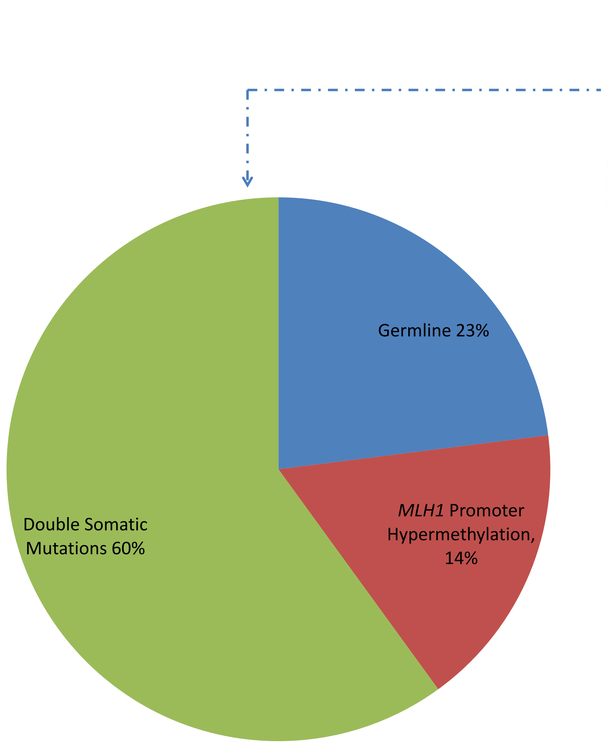
METHODS

- A retrospective analysis was performed on data from colorectal and endometrial cancer patients with abnormal IHC who had paired tumor/germline MMR gene analysis between 12/05/16-09/07/17.
- Results of sequencing and deletion/duplication analyses of the MMR genes and *EPCAM* (del/dup only), *MLH1* promoter hypermethylation, and microsatellite instability (MSI) were assessed.

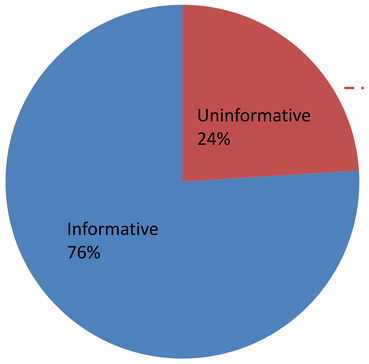
CASE DETAILS

	Number	Percent Total
Total Cases	136	100%
No Previous Germline Testing	97	71%
Previous Germline Testing	39	29%
Colorectal Cancer	69	51%
Endometrial Cancer	67	48%
Average Age of Onset in Years	59	-
Met Revised Bethesda Criteria	35	33%
Met Amsterdam I Criteria	7	5%

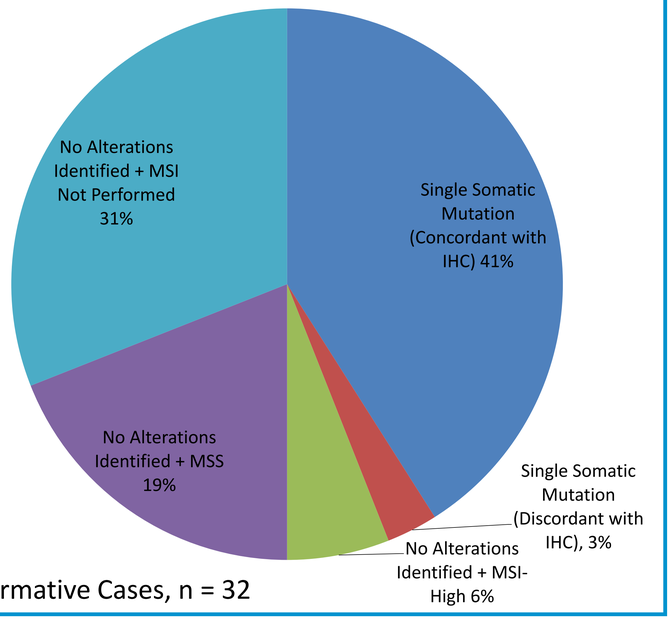
RESULTS



Informative Cases, n = 104



Total Cases, n = 136



Uninformative Cases, n = 32

RESULTS

Molecular DNA Results	Concordant with IHC?	Diagnosis	No Previous Testing (n)	Previous Testing (n)	n (%)
Germline mutation	Yes	Lynch Syndrome	21	3	24 (18%)
MLH1 promoter hypermethylation	Yes	IHC likely due to somatic changes	15	3	18 (13%)
Informative cases explained by traditional testing algorithm			***36***	***6***	***42 (31%)***
Double somatic mutations*	Yes	IHC likely due to somatic changes	37	18	55 (40%)
Double somatic mutations in *MLH1*/presence of *MLH1* promoter hypermethylation and loss of *PMS2* on IHC	No	IHC likely due to somatic changes	4	2	6 (4%)
Double somatic mutations + germline VUS**	Yes	IHC likely due to somatic changes	0	1	1 (1%)
Informative cases explained by tumor MMR analyses			***41***	***21***	***62 (45%)***
Total Informative Cases			**77**	**27**	**104 (76%)**

Molecular DNA Results	Concordant with IHC?	No Previous Testing (n)	Previous Testing (n)	n (%)
Single somatic mutation identified	Yes	6	7	13 (10%)
Single somatic mutation in another gene identified	No	1	0	1 (1%)
No alterations + MSI-High	No	0	2	2 (1%)
No alterations + MSS	No	3	3	6 (4%)
No alterations + MSI not performed	No	10	0	10 (7%)
Total Uninformative Cases		**20**	**12**	**32 (24%)**

* One case was an apparent hyper/ultramutator phenotype
** Lynch syndrome could not be fully ruled out

TAKE-HOME POINTS

- Adding tumor MMR gene analyses to the Lynch syndrome testing algorithm allows for potential exclusion of Lynch syndrome and reduces the likelihood of unexplained IHC results.
- In this cohort 76% of patients had either a germline MMR mutation, consistent with Lynch syndrome, or somatic changes to explain IHC results, significantly reducing the likelihood of Lynch syndrome in the majority of cases.
- In this cohort, 45% of cases would have remained unexplained without the addition of somatic MMR gene sequencing and deletion/duplication analyses.