Unsuspected Lynch Syndrome due to Pathogenic Variants in MSH6 and PMS2

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Methods

- The pan-cancer panel included the following 25 genes: *APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2,* ***EPCAM, MLH1, MSH2, MSH6****, MUTYH, NBN, PALB2,* ***PMS2****, PTEN, RAD51C, RAD51D, SMAD4, STK11*, and *TP53*.
- The sample consisted of 200,430 individuals selected by their providers for suspicion of Hereditary Breast and Ovarian Cancer (HBOC) or Lynch syndrome (LS).
- PVs were defined as mutations with a laboratory classification of deleterious or suspected deleterious.
- All clinical data was obtained by health care provider report on the test request forms.

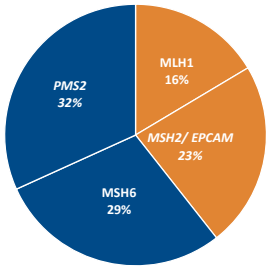
Methods

The prevalence of PVs in each of the MMR genes was determined in:

- The overall testing cohort (N=200,430)
- Cases where providers indicated ascertainment for suspicion of LS (N=19,728)
- Cases submitted with a clinical history meeting current NCCN LS testing guidelines* (N=44,774)

*The patient or a first- or second-degree relative met revised Bethesda criteria or had a diagnosis of endometrial cancer under age 50.

Distribution of Lynch Syndrome Genes

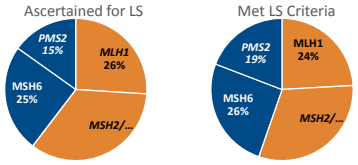


Gene	N	%
Patients Tested	200,430	–
MLH1	307	0.15%
MSH2/EPCAM	429	0.21%
MSH6	539	0.27%
PMS2	594	0.30%
Total	1866*	0.93%

*3 Patients had a mutation in 2 Lynch syndrome genes

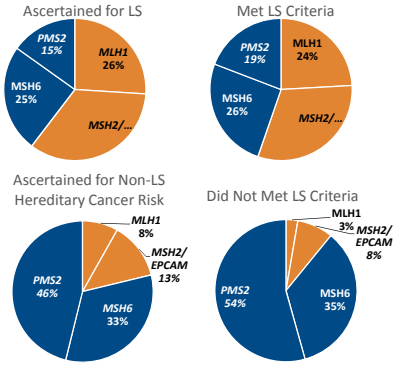
In the overall testing cohort, the proportion of pathogenic variations in *PMS2* and *MSH6* is higher than in *MLH1* and *MSH2*.

Distribution of Lynch Syndrome Genes



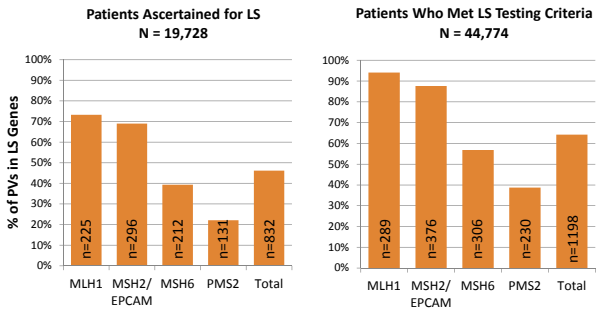
- More than half of pathogenic variants in patients with a clinical indication for Lynch Syndrome are in *MLH1* and *MSH2*.

Distribution of Lynch Syndrome Genes



- More than half of pathogenic variants in patients with a clinical indication for Lynch Syndrome are in *MLH1* and *MSH2*.
- The majority of pathogenic variants in patients without clinical indication for Lynch Syndrome were in *MSH6* and *PMS2*.

LS PVs by Ascertainment &Testing Criteria



2 patients ascertained for LS had 2 PVs in different LS genes

3 patients who met LS testing criteria had 2 PVs in different LS genes

Conclusions

- PVs in *MSH6* and *PMS2* are a more common cause of LS than previously estimated, regardless of whether individuals are ascertained for suspicion of LS, or meet LS testing guidelines.
- Current testing practices and LS criteria identify the majority of individuals with LS caused by PVs in *MLH1* and *MSH2/EPCAM*, but miss close to 50% of individuals with LS due to PVs in *MSH6* and *PMS2*. This suggests that "unexpected" LS findings with panel testing are most likely due to the reduced likelihood that genes with lower penetrance will reliably manifest in the patient's personal and family history.
- These findings demonstrate the potential value of inclusion of LS gene testing for all patients being assessed for inherited cancer risk even in the absence of a history suspicious for LS. This consideration applies to other hereditary cancer genes conferring moderate, but clinically actionable, cancer risks.