Concordance of Germline Multigene Panel Testing with Prior Microsatellite Instability and Immunohistochemistry Analyses in Endometrial Cancer Patients

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Objectives: Microsatellite instability (MSI) and immunohistochemistry (IHC) for the mismatch repair (MMR) proteins are recommended methods of screening for Lynch syndrome and eligibility for targeted therapy, but their sensitivity and specificity are each less than 90%. We aimed to assess the concordance of germline multigene panel testing (MGPT) results with prior MSI and/or IHC in endometrial cancer patients.

Methods: Cases with endometrial cancer who had MGPT between 2012 and 2016 at a single laboratory and reported results of prior MSI and/or IHC were reviewed and classified as concordant if tumor testing matched MGPT results, discordant if they did not match MGPT results, and atypical if they had both concordant and discordant features.

Results: Of cases with IHC results (n=739), concordance was high among those with normal IHC (96%, n=278) and low among those with abnormal IHC (19.8%, n=89). The largest percentage of cases with abnormal IHC, were discordant cases for which MLH1 methylation had not been ruled out (43.3%, n=195). An additional 31.6% (n=142) were discordant with methylation ruled out or not necessary, and 5.3% (n=24) were atypical. Concordance rates further varied by IHC pattern (see Table). Of note, ten cases with concordant, normal IHC had a germline mutation in a non-MMR gene and 7 of 11 discordant cases with normal IHC had a germline MMR mutation.

Conclusions: Sporadic MLH1 promoter methylation is known to be common in endometrial cancer. These results highlight the importance of ruling this out in order to decrease discordant and/or inconclusive results. Other possible explanations for discordant results include two somatic MMR mutations, unclassified variants which are actually pathogenic, mutations not detected with current technology, and inaccurate tumor testing. Endometrial cancer patients with normal IHC will most likely have normal germline testing results; however, a small percentage may still have Lynch syndrome and potentially, a MMR deficient tumor eligible for a PD1 inhibitor. MLH1 methylation analysis, germline MGPT, and tumor MMR gene sequencing is likely to result in few discordant results and more conclusive answers for endometrial cancer patients with MMR deficient tumors.

Table. Concordance of Endometrial Cancer Cases by IHC Pattern (n=739)

IHC Results and Concordance	N	%
Normal IHC	289	39.1%
Concordant	*278*	*96.2%*
Discordant	*11*	*3.8%*
Abnormal IHC	450	60.9%
Concordant	*89*	*19.8%*
Discordant	*142*	*31.6%*
Atypical	*24*	*5.3%*
Discordant-Methylation not ruled out	*195*	*43.3%*
Loss of MLH1 (with or without PMS2)	245	54.5%
Concordant	*36*	*14.7%*
Discordant	*15*	*6.1%*
Discordant-Methylation not ruled out	*195*	*79.2%*
Loss of PMS2 only	37	8.2%
Concordant	*4*	*10.8%*
Discordant	*33*	*89.2%*
Loss of MSH2 (with or without MSH6)	71	15.8%
Concordant	*22*	*31.0%*
Discordant	*48*	*67.6%*
Atypical	*1*	*1.4%*
Loss of MSH6 only	65	14.4%
Concordant	*27*	*41.5%*
Discordant	*38*	*58.5%*
Atypical staining pattern*	32	7.1%
Concordant	*0*	*0.0%*
Discordant	*8*	*25.0%*
Atypical	*23*	*71.9%*
Discordant-Methylation not ruled out	*1*	*3.1%*

*Loss of two proteins that are not part of the same heterodimer, loss of three or more proteins, or equivocal, weak, or focal staining