Lynch Syndrome Testing Algorithm

Patient with personal or family history of cancer suspicious for Lynch syndrome

Has genetic testing been previously performed on family member?

Pathogenic mutation identified

Consider FMTT / Familial Mutation, Targeted Testing for known mutation in family

Testing in family member was negative or variant of uncertain significance identified

Consider LYNCH / Lynch Syndrome Panel or testing for the variant of uncertain significance in family member to determine if it segregates with disease

Is patient’s tumor available for testing?

YES

NO

NO

Patient with personal or family history of cancer suspicious for Lynch syndrome

MSI-H and loss of MLH1/ PMS2 on IHC staining

Patient is young (<50) or family history suggestive of Lynch syndrome

Consider MLH1Z / MLH1 Gene, Full Gene Analysis

If negative consider MLH1Z / MLH1 Gene, Full Gene Analysis

If endometrial tumor: consider ML1HM / MLH1 Hypermethylation Analysis, Tumor

If colorectal tumor: consider BRMLH / MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor

No hypermethylation

Hypermethylation

Hypermethylation and BRAF negative

Hypermethylation and BRAF positive

Sporadic in origin OR if still suspicious of Lynch syndrome consider MLHPB / MLH1 Hypermethylation Analysis, Blood on blood specimen

Sporadic in origin; no further testing recommended

Consider performing both MLH1Z / MLH1 Gene, Full Gene Analysis and PMS2Z / PMS2 Gene, Full Gene Analysis to detect germline mutation

NO

Teenager onset (<50)

MSI-H and loss of MLH1/ PMS2 on IHC staining

Patient is older (>50) and family history is not suggestive of Lynch syndrome

MSI-H and loss of PMS2 on IHC staining

Consider PMS2Z / PMS2 Gene, Full Gene Analysis

Consider MSH6Z / MSH6 Gene, Full Gene Analysis and MSH2Z / MSH2 Gene, Full Gene Analysis

If negative consider MSH6Z / MSH6 Gene, Full Gene Analysis

MSI-L or MSS and intact protein expression on IHC

MSI-H and loss of MSH2 / MSH6 on IHC staining

MSI-H and loss of MSH2 / MSH6 on IHC staining

If negative consider MSH2Z / MSH2 Gene, Full Gene Analysis

If negative consider MSH2Z / MSH2 Gene, Full Gene Analysis

Consider larger panel testing such as HCRC / Hereditary Colon Cancer Multi-Gene Panel

Sporadic in origin OR if still suspicious of Lynch syndrome consider MLHPB / MLH1 Hypermethylation Analysis, Blood on blood specimen

Sporadic in origin; no further testing recommended

Consider performing both MLH1Z / MLH1 Gene, Full Gene Analysis and PMS2Z / PMS2 Gene, Full Gene Analysis to detect germline mutation

IHC=Immunohistochemical
MSI=Microsatellite Instability
-MSI-H=MSI-High
-MSI-L=MSI-Low

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