Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer (HNPCC)) – OMIM #120435 120436 (MLH1), 609309 (MSH2), 600678 (MSH6)

INTRODUCTION
Lynch syndrome (also known as HNPCC) is an autosomal dominant cancer predisposition syndrome characterised by colorectal adenocarcinomas and other cancers including; endometrial, ovary, stomach, urinary tract and brain. The mean age of onset for Lynch syndrome is ~45yrs, but it can develop as early as teenage. Age related penetrance is seen in Lynch syndrome mutation carriers but the lifetime risk for of developing an associated cancer is ~70-80%. Women are at higher risk of developing endometrial cancer than colorectal cancer. Lynch syndrome is caused by inactivating mutations in the mismatch repair (MMR) genes, resulting in defective DNA mismatch repair which may often be detected by microsatellite instability (MSI) within tumour DNA. Approximately 98% of Lynch syndrome is caused by pathogenic mutations in the genes, MLH1, MSH2 and MSH6.

TESTING
- Diagnostic: Clinically affected patients.
- Presymptomatic: Individuals at risk of developing Lynch syndrome. Clinically unaffected relatives of individuals in whom a pathogenic MMR gene mutation has been identified.

REFERRALS
- All diagnostic & presymptomatic cases must be referred through Clinical Genetics departments.
- Diagnostic referrals should meet a minimum of “Modified Amsterdam Criteria”.
- Requests for presymptomatic testing should either be discussed with the laboratory in advance or be accompanied by details regarding the known pathogenic mutation in the family.

STRATEGY
- Diagnostic testing includes screening of the entire coding region and intron/exon boundaries of the MLH1, MSH2 and MSH6 genes and dosage analysis for large scale rearrangements of these 3 genes and the EpCAM gene, which is upstream of MSH2 (Kovacs et al. 2009, Human Mutation, 30(2):197-203).
- In mutation negative cases showing loss of MSH2 and MSH6 on immunohistochemistry, testing for a previously reported inversion of MSH2 can be conducted (Rhees et al. 2014, Familial Cancer, 13:219-225).
- When a pathogenic mutation has been identified in an individual, subsequent testing of family members (presymptomatic or diagnostic confirmation) involves testing for the familial mutation only.

TECHNICAL INFORMATION
- Mutation screening is undertaken by direct fluorescent sequencing of the entire coding region and intron/exon boundaries of MLH1, MSH2 and MSH6. Dosage analysis is carried out by MLPA (multiplex ligation-dependant probe amplification) of the MLH1, MSH2 and MSH6 genes and the EpCAM gene which is upstream of MSH2; using kits P003-B2 and P072-B2 from MRC-Holland.
- MSI analysis and immunohistochemistry of tumour samples may assist in the diagnosis of Lynch syndrome particularly in patients who fail to meet the testing criteria or patients in whom no MSH1/MSH2 mutation has been found. MSI analysis is available in this laboratory and IHC analysis is available in cellular pathology.

CLINICAL SENSITIVITY
Germline MLH1 and MSH2 mutations account for ~90% of mutations in families with Lynch syndrome; MSH6 mutations ~7%-10%; and PMS2 mutations in fewer than 5%. Germline deletions in EPCAM (not a MMR gene) inactivate MSH2 in ~1% of individuals with Lynch syndrome (Kohlmann, 2014 http://www.ncbi.nlm.nih.gov/books/NBK1211/).

TARGET REPORTING TIMES
- Diagnostic test (3 gene screen): 40 working days
- Presymptomatic/Familial Mutation test: 10 working days

N.B. Details are correct for the date of printing only – last update 11/06/2015