Q: Which individual within a multi-case family should be investigated?
If there are multiple living affected individuals available in a family, preference for individual to be investigated is as per the following order:
   a. youngest colorectal cancer (age <60)
   b. endometrial cancer (age <60)
   c. other Lynch tumour (age <60)
   d. colorectal cancer (age <75)
   e. endometrial cancer (age <75)
   f. other Lynch tumour (age <75)
When undertaking IHC, always confirm on the pathology report that the tissue studied is the appropriate sample from an invasive cancer.

Q: When should Lynch investigations be undertaken in a second family member?
All cases should be discussed at the MDT. Lynch investigations in an additional family member is advised if:
   i) the first proband’s tumour proves to be demonstrated as ‘sporadic’ (IHC normal/ BRAF mutation present) and the following criteria are met:
      • Residual family history excluding the tested individual meets Lynch testing criteria AND
      • Second living affected individual available to test
      Proceed with IHC and follow protocol 3 in the second individual
   ii) if there has been an abnormality on IHC and sequencing/MLPA of appropriate genes has not revealed a pathogenic mutation and the following criteria are met:
      • Residual family history excluding the tested individual meets Lynch testing criteria AND
      • Tumour material available from second affected family member (alive OR deceased)
      Proceed with IHC and BRAF (if loss of MLH1 and/or PMS2) in the second individual’s tumour. Do not undertake germline mutational testing in the second individual. If IHC of the tumour in the second family member shows concordance for the same IHC abnormality as the proband, consider advanced tests such as:
      • Tumour promoter hyper-methylation studies (for loss of MLH1+-/ PMS2)
      • Karyotype (for loss of MSH2/MSH6)
Q: When should Lynch investigations be initiated in a family with no living affected individuals?
Lynch investigations should be offered to a family in which there are no living affected individuals if:

- The unaffected consultand is the FDR of an individual affected with a CONFIRMED Lynch tumour (LT) <75
- AND in total there are 3 or more individuals affected with a Lynch tumour in the family who are FDR/SDR of each other AND at least two affected individuals are FDR of each other.
- AND at least one case is CRC/endometrial cancer.
- AND one individual was affected <50

If there is tumour material available for an affected individual in the family, then the optimal first-line investigation is IHC in this tumour material (+BRAF if loss of MLH1+/PMS2).

- If there is abnormality on this IHC, sequencing of the appropriate gene(s) should be offered to the consultand.
- If IHC is normal, no further tests should be offered

If there is no tumour material available for affected family members, sequencing of MLH1/MSH2/MSH6 can be offered to the unaffected consultand.

Q: Can an individual with a non-invasive polyp be investigated for Lynch
Non-invasive polyp material should not be studied unless there is no other living affected individual to investigate. A proband with a polyp should only be investigated if the following criteria are met:

- The proband is <50 AND
- There is a FDR with a LT <60 AND
- The polyp is adenomatous AND
- The polyp is >5mm AND
- The polyp is villous/tubulovillous OR shows moderate-to-severe dysplasia OR is located proximal to the splenic flexure

Q: Can germline mutational testing be undertaken in an affected individual if tumour studies have not been performed?
It is appropriate to proceed directly to germline mutational testing of MLH1+MSH2+MSH6 when:

- the tumour tissue is unavailable from an affected individual treated in the past and there is no other living affected individual with tumour tissue available
- the affected individual has had invasive cancer confirmed on biopsy, it is not possible to perform IHC on the biopsy and investigation is helpful to inform surgery.

AND

If the following criteria are met:

- The individual is <50 AND
- the family meets Lynch testing criteria AND
- there is a total of ≥2 family members affected
Q: How should an unclassified variant in a MMR gene be managed?
Rare missense variants in MLH1, MSH2, MSH6 and PMS2 are common in the general population. The variant should be submitted for further evaluation via vus@icr.ac.uk and discussed at MDT.

Q: Should MLH1 germline mutational testing be undertaken if there is isolated loss of PMS2?
Yes. If the tumour is BRAF wildtype and germline mutational testing of PMS2 is normal. This is because there can be false positive staining of MLH1. Series have detected a frequency of pathogenic germline mutations in MLH1 in individuals with apparently isolated loss of PMS2 in the tumour.

Q: Should PMS2 germline mutational testing be undertaken if there is loss of MLH1+PMS2 and no germline mutation in MLH1 is detected?
No. Series have detected no appreciable frequency of pathogenic germline mutations in PMS2 in individuals with loss of MLH1+PMS2.

Q: Should BRAF testing be undertaken in tissue from any Lynch tumour?
BRAF testing should only be undertaken in tissue from invasive colorectal cancer when there is loss of MLH1+/- PMS2. BRAF mutations do not arise in other tumours such as endometrial cancer when there is loss of MLH1+/- PMS2.

Q: When should tumour promoter hypermethylation studies be undertaken?
Promoter hypermethylation studies should not be undertaken routinely. Tumour promoter hypermethylation studies should only be undertaken following discussion at the MDT and when
- There is concordance for MLH1 +/- PMS2 loss in two affected individuals in the family and germline mutational testing has not found a pathogenic mutation. Both samples should have been demonstrated as BRAF wildtype.
- A rare variant detected in MLH1, classified following MDT discussion as uncertain pathogenicity that requires further evaluation.

Q: When should MSI testing be undertaken?
MSI should not be undertaken routinely. It may be performed in occasional scenarios, following discussion at the MDT.

Q: What is hyperplastic polyposis syndrome:
As per the by the WHO criteria, Hyperplastic polyposis is defined as:
- at least 30 pan-colorectal hyperplastic polyps OR
- at least 5 hyperplastic polyps proximal to the sigmoid colon of which at least 2 are > 10 mm in diameter OR
- any number of hyperplastic polyps in a patient who has a first degree relative with hyperplastic polyposis

Q: When should aspirin be recommended
As per combined expert opinion, (Cancer Genetics Group December 2012), Aspirin should be recommended for those at high-moderate risk or greater (that is those in B2, B3 or B4 surveillance groups). The evidence for the optimum age at which to commence aspirin is unclear but it was agreed at this meeting that aspirin should be commenced no earlier than
colonoscopy. When aspirin is recommended, decision regarding administration is made on a per-case basis by GP in accordance with co-morbidities.

**Q:** What surveillance should be offered for individuals who have had colorectal cancer and have a family history of colorectal cancer?
These individuals should be offered additional surveillance on the basis of their family history beyond the standard follow-up from their cancer. This can be assessed on Protocol 8 by counting the consultand as a FDR in the assessment.

**Q:** What surveillance should be offered for polyps (outside of mutation-positive individuals)?
Surveillance should be offered as per the recommendations in “Surveillance guidelines after removal of colorectal adenomatous polyps” Atkins and Saunders, Gut 2002 which remained unchanged in the updated guidance “Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002)” Cairns et al 2010

**Q:** What program of screening is offered within the National Bowel Cancer Screening Programme
FOB kits are sent out biennially to all individuals age≥ 60. Individuals with abnormal results are offered colonoscopy. One-off flexible sigmoidoscopy at 55 is due to be introduced soon as part of the NBCSP.