Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

Colorectal cancer genetic screening

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Sample Required
Paraffin embedded tumour tissue

- **>20% tumour:** 5 x 10µm sections in a clean universal
- **<20% tumour**: 10 x 5µm slide mounted sections along with H&E with regions of >20% tumour highlighted

If available, a normal tissue block or blood sample (5ml EDTA) to be sent to aid analysis.

Samples should be accompanied by a FULLY completed Molecular Pathology request form (available from the laboratory or www.nbt.nhs.uk/genetics)

All samples should be labelled with patient name, date of birth and pathology block number

Consent and Storage:
All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

MSI (microsatellite instability) occurs in 10-20% of patients with a diagnosis of colorectal cancer. MSI may be detected using molecular / genetic analysis or immunohistochemistry of the mismatch repair genes. The detection of MSI determines:

(a) That stage II patients should not be treated with chemotherapy, as they are unlikely to respond[1].
(b) Patients are more likely to respond to immunotherapy[2].
(c) Tumours should be further tested for the *BRAF* p.V600E mutation and *MLH1* promoter methylation to determine if the tumour is sporadic or associated with Lynch syndrome[3].

Lynch syndrome accounts for 3-6% of colorectal cancer (CRC) and is associated with mutations in the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). A screening test for tumour microsatellite instability (MSI) is helpful in targeting families suitable for MMR gene testing, as MSI-High status increases the likelihood that a MMR mutation will be detected.

BRAF p.V600E mutation testing and *MLH1* promoter methylation testing also assists in stratification as the presence of both in an MSI-High tumour is suggestive of a tumour of sporadic origin.

Service Offered

- Microsatellite instability is detected using the MSI Analysis System, Version 1.2 (MD1641 Promega).

If MMR IHC has already been performed (and shows loss of protein), it is acceptable to send samples for BRAF / MLH1 methylation analysis alone

- The c.1799T>A p.(Val600Glu) mutation in *BRAF* is detected by pyrosequencing. This assay can detect 5% p.(Val600Glu) in a background of wildtype DNA.
- *MLH1* promoter hypermethylation testing is carried out by methylation specific pyrosequencing.

Referrals

- Referrals are accepted from Clinical Genetics, Oncologists or Histopathology Consultants.
- For sample requirements please refer to the information on the left.

Clinical Advice

If clinical discussion is required, we would recommend contact with Dr Newton Wong, Consultant Histopathologist, Southmead Hospital.

Target Reporting Times

- MSI testing to inform treatment: 7 days
- MSI testing (+/- *BRAF/MLH1*) for Lynch pre-screening: 14 days
- *BRAF*/*MLH1*: 7 days

Quality

BGL participates in the *GENQA* scheme for this service.

References

1. Sargent DJ, Marsoni S, Monges G, *et al*: Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 28:3219-3226, 2010
2. Le DT, Uram JN, Wang H, *et al*: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509-2520, 2015
3. Molecular testing strategies for Lynch syndrome in people with colorectal cancer. NICE Diagnostics guidance [DG27] Published date: February 2017.

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