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# Service information: Familial Adenomatous Polyposis (FAP)

**Gene/Locus:** *APC, MUTYH* **OMIM:** #175100/*611731 (*APC*), #608456/*604933 (*MUTYH*)

**Referrals:** Accepted from **Clinical Geneticists** only

**Testing:** Diagnostic testing offered in clinically affected patients, presymptomatic testing in individuals with a family history of pathogenic or likely pathogenic *APC/MUTYH* variants. Carrier testing in individuals with a family history of pathogenic or likely pathogenic *MUTYH* variants or individuals whose partners carry a pathogenic or likely pathogenic *MUTYH* variant(s).

## Target Reporting Times:

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|---|---|
| • Diagnostic screening | 56 calendar days |
| • MLPA only diagnostic | 28 calendar days |
| • Predictive testing for known pathogenic/likely pathogenic variants | 14 calendar days |
| • Confirmatory testing for known pathogenic/likely pathogenic variants | 28 calendar days |
| • Carrier testing for known pathogenic/likely pathogenic *MUTYH* variants | 28 calendar days |
| • Carrier screen for *MUTYH* variants | 28 calendar days |

## Test Details:

- **Diagnostic screening for *APC*/*MUTYH* mutations:** Next generation sequencing (NGS) of all coding sequence and intron/exon boundaries of *APC* and *MUTYH*. Confirmations and repeats tested using Sanger sequencing.
- **Carrier screening *MUTYH* variants:** Sanger sequencing to cover all coding sequence and intron/exon boundaries of *MUTYH*.
- **Testing for known pathogenic and likely pathogenic variants** in individuals with a family history of *APC/MUTYH* mutations, by Sanger sequencing or MLPA, as appropriate.

## MLPA testing:

Dosage analysis only by MLPA can be offered for *APC* and *MUTYH* exons 1, 2 and 7 (P043).

## Service Details:

Based on in-house test validation the sensitivity of NGS testing is estimated to be greater than 98.6%. If a pathogenic or likely pathogenic variant is not detected by the testing procedure, a diagnosis of FAP cannot be excluded, as the patient may have a mutation in another gene or in a region of the gene(s) not covered by the above analysis.

## Sample Requirements:

- **EDTA** blood sample (≥4 ml), labelled with patient's **full name**, **date of birth** and **NHS number**, or genomic DNA (≥7.5µg at ≥50 ng/µl). Please send two separate blood/DNA samples for presymptomatic testing.
- Samples should be accompanied by a **fully** completed referral card which should include the patient's full name, date of birth and NHS number.
- Please also include details of the gene(s) to be tested, relevant clinical details and full details of the referring clinician and centre.
- Familial positive control samples are required for presymptomatic/carrier testing, if available.

## Consent:

Please note that in submitting a sample, it is the responsibility of the clinician to ensure that consent has been taken i) for testing, ii) for storage, and iii) for the use of this sample and the information generated to be shared with the patient's relatives and their health professionals. Following testing, a sample of the patient's DNA may also be used anonymously to validate new tests and for internal quality control purposes.

## NGS Testing information.

NGS of all coding sequence and intron/exon boundaries (-30 to +15) of selected genes using a Sophia Genetics Custom HCS Panel and Illumina MiSeq platform. Data analysis using MiSeq Reporter software for FASTQ file generation followed by Sophia DDM for alignment of reads to genome build GRCh37, coverage analysis and variant calling.

The target region is covered at a minimum depth of 30x. Thresholds for variant calling: ≥15% total reads for indels and ≥20% total reads for single nucleotide variants (SNVs). Based on in-house test validation the analytical sensitivity of this testing is estimated to be greater than 98.6%. Variant confirmations and repeats are performed using Sanger sequencing. Copy number variation (CNV) confirmation by multiplex ligation-dependent probe amplification (MLPA).

*If information on the coverage of individual genes is required, please contact the laboratory. Variants will be classified based on the ACMG variant interpretation guidelines (Richards et al (2015) Genet Med. 17:405-24; Ellard et al (2017) ACGS Best Practice Guidelines for Variant Classification 2017).Sequence variants defined by the laboratory as benign or likely benign variants are recorded but not reported. In some cases variants of uncertain clinical significance with no convincing evidence for pathogenicity may not be reported. NGS sequence data on other genes on the Sophia Genetics Custom HCS Panel that are not requested at the time of referral will be stored but not analysed.*

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