Polyposis Panel:

Familial Adenomatous Polyposis (FAP, AFAP) – OMIM 175100;
MUTYH- associated Polyposis (MAP) – OMIM 608456;
Juvenile Polyposis Syndrome (JPS) – OMIM 174900;
POLE- related susceptibility to colorectal cancer (CRC) – OMIM 615083;
POLD1- related susceptibility to CRC (OMIM 174761)

Background

The initial symptom for this group of conditions is multiple colorectal adenomas (polyps); patients are at a high risk of developing colorectal cancer.

Patients with FAP have hundreds or thousands of polyps in the bowel, that start to appear during their teens (although there may not be any physical symptoms initially); if left untreated, cancer usually develops by the age of 40. FAP is caused by pathogenic variants in the *APC* gene (OMIM 611731) and has an autosomal dominant inheritance pattern, so there is a 50% chance of a parent with the pathogenic variant passing it onto their child. Some *APC* variants result in attenuated FAP (AFAP); patients have fewer polyps (less than100) and develop cancer later.

Patients with MAP have polyps that do not appear until adulthood and are less numerous than those found in patients with FAP. MAP is caused by pathogenic variants in the *MUTYH* gene (also called *MYH*; OMIM 604933), and is autosomal recessive (both copies of the gene are mutated in affected individuals). Several studies indicate that 20-30% of patient with >10 adenomas, no *APC* gene variant and no dominant transmission have variants in the *M UTYH* gene.

Patients with JPS have multiple juvenile hamartomatous polyps throughout the gastrointestinal (GI) tract. Polyps usually begin to appear in the first decade of life and patients can develop between five to hundreds of polyps over their lifetime. JPS is caused by a pathogenic variant in the *SMAD4* gene (OMIM 600993) or *BMPR1A* gene (OMIM 601299), it has an autosomal dominant inheritance pattern.

Pathogenic variants within the polymerase proofreading domains of the *POLE* gene (OMIM 174762) and *POLD1* gene (OMIM 174761) have been reported to be associated with CRC and polyposis. Patients present with either a few or multiple polyps. It has an autosomal dominant inheritance pattern.

Once these conditions have been confirmed, regular bowel screening is important.

Recommended Clinical Referral Criteria

Requests for testing will only be accepted from the clinical genetics service. These referrals will include:

- Patients/families with multiple colorectal adenomas or a family history of multiple colorectal adenomas
- Patients with congenital hypertrophy of the retinal pigment epithelium (CHRPE) and a family history of bowel cancer. Individuals with an *APC* pathogenic variant have a 50% risk of developing CHRPE

- Predictive/carrier testing for relatives of individuals found to have pathogenic variants in *APC*, *MUTYH, BMPR1A*, *SMAD4, POLE* (exon 13) or *POLD1 (*exon 12).

Individuals with a personal or family history of polyposis that fulfils the testing criteria above can be referred to the All Wales Medical Genomics Service for familial cancer risk assessment and genetic testing. Individuals with a significant personal or family history of polyposis that does *not* fulfil the genetic testing criteria *may* still benefit from a familial cancer risk assessment and can be referred to the All Wales Medical Genomics Service.

Information on making a cancer genetics referral is available here.

The general guidelines for referral to clinical genetics are available here.

Molecular Analysis and Turnaround Times (TATs)

Prices available on request, please contact the laboratory using details below*.

Test	Details	TAT (calendar days)
Next generation sequencing (NGS) and dosage analysis	*APC*, *MUTYH, BMPR1A* and *SMAD4* are enriched using an Illumina TruSight Cancer assay and sequenced on an Illumina NextSeq. *APC* will be completely sequenced, gaps will be filled using Sanger sequencing. For the remaining genes common gaps will be filled using Sanger sequencing, where gaps remain coverage will be reported. Dosage analysis will be carried out by NGS. Sanger sequencing will be carried out for *POLE* exon 13 and *POLD1 e*xon 12 only.	42 CD
Familial follow-up	Testing for known familial pathogenic variants in *APC*, *MUTYH, BMPR1A*, *SMAD4, POLE* (exon 13) and *POLD1 (e*xon 12) for parental and variant investigations. Testing for spouses of MAP affected or carrier individuals for common *MUTYH* pathogenic variants.	42 CD
Pre-symptomatic testing	Pre-symptomatic testing for known familial pathogenic variants in *APC*, *MUTYH, BMPR1A*, *SMAD4, POLE* (exon 13) and *POLD1 (e*xon 12).	28 CD

***Please note screening and dosage analysis of individual genes in the polyposis panel can be requested.**

Sample requirements

Blood: 5ml in EDTA. Please label samples with three identifiers and date of collection. Please contact lab prior to sending a prenatal sample. All samples must

be accompanied by a request form. Consent for testing & DNA storage is assumed when request for test received.

Contact Details

All Wales Genomics Laboratory,
Institute of Medical Genetics,
University Hospital of Wales,
Heath Park,
Cardiff, CF14 4XW
Tel: 029 2184 2641
Fax: 029 2184 4043
lab.genetics@wales.nhs.uk
http://www.medicalgenomicswales.co.uk

Links and Support

Orphanet: http://www.orpha.net/
OMIM: http://www.omim.org/
Genetic Test Registry: http://www.ncbi.nlm.nih.gov/gtr/
Support: http://www.fapgene.com
http://www.bowelcanceruk.org.uk