Hereditary Colorectal Cancer (CRC)

Tests available

- Lynch Syndrome
- Polyposis Syndrome
- Hereditary CRC High Risk genes
- Hereditary CRC Comprehensive Multigene Panel

Contact Asia Genomics for a copy of a Genetic Test Brochure

Colorectal cancer is the 4th most common malignancies diagnosed in North America (Siegel et al, 2013). In Singapore, it is the most common malignancy affecting men and second most common to affect women (Singapore Cancer Registry, 2015). Like most cancers, the majority of colorectal cancer (CRC) cases occur sporadically with up to 6% having a hereditary basis (NCI, 2015) (figure 1). Lynch syndrome also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC) is the most common form of inherited CRC, accounting for up to 4% of all CRC cases (Aaltonen et al, 1998; Lynch and de la Chapelle, 2003). Familial Adenomatous Polyposis (FAP) and attenuated FAP (AFAP), on the other hand, accounts for up to 1% of all CRC cases (NCCN, 2014). The remaining hereditary cases are due to MUTYH-Associated Polyposis, and other rare syndromes (NCCN, 2014).

Colorectal tumours can be classified into three groups according to the lesion (NCI, 2015):

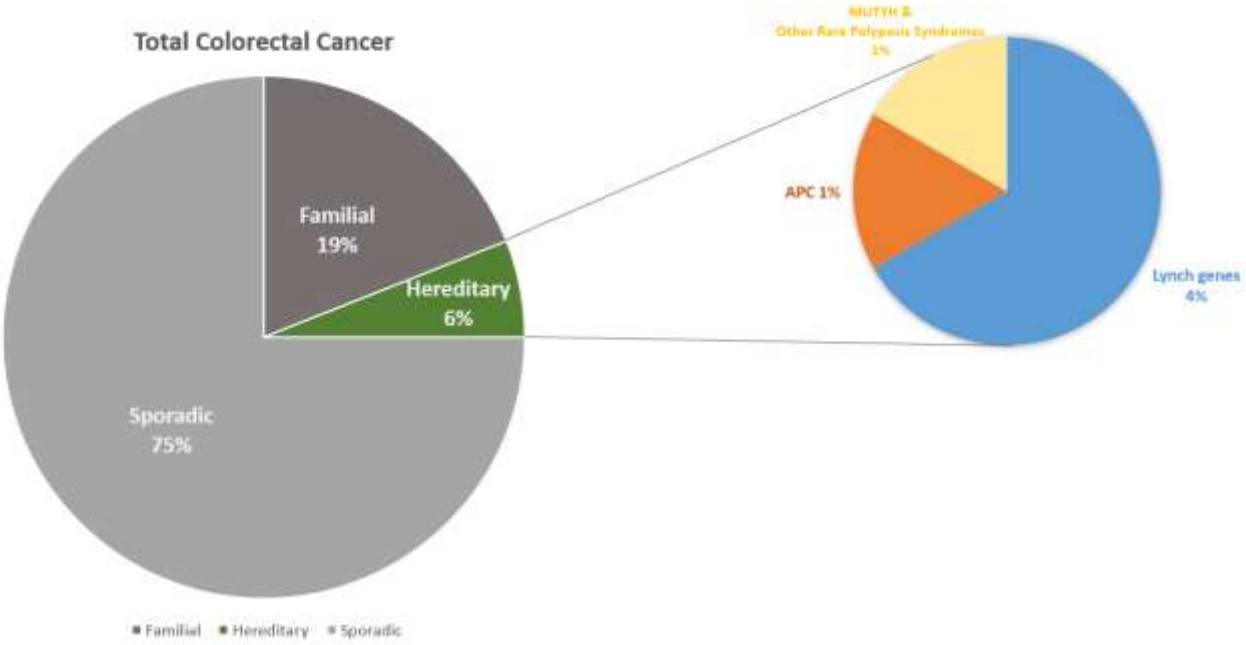
1. Non-neoplastic polyps (hyperplastic, juvenile, hamartomatous) or benign growth
2. Neoplastic polyps (adenomatous polyps and adenomas)
3. Cancers

Despite the classification as non-neoplastic polyps, studies suggest increased CRC risk in families with juvenile polyposis (JPS), Peutz-Jeghers syndrome (PJS), and hyperplastic polyposis (Howe et al, 1998; Jeevaratnam et al, 1996; Rashid et al, 2000).

Persons with neoplastic polyps like adenomas are also thought to be at increased risk for CRC according to epidemiological data, and it has generally been thought that adenomas are the precursors to CRC (Shinya and Wolff, 1979; Fenoglio and Lane, 1974; Morson, 1974; Muto et al, 1975; Stryker et al, 1987).

Over 95% of CRC are carcinomas, of which 95% are adenocarcinomas which are generally recognised as benign growth with potential to transform.

Figure 1.



The National Comprehensive Cancer Network (NCCN, 2014) published testing criteria for Hereditary CRC (including Lynch and Polyposis Syndromes) include the following

For Lynch Syndrome

- Family history of a known Lynch syndrome mutation (MLH1, MSH2, MSH6, PMS2, EPCAM)
- Patient has a cancer on the Lynch syndrome tumor spectrum that demonstrates microsatellite instability (MSI-H) or absence of a mismatch repair protein via immunohistochemistry (IHC)
- Patient diagnosed with endometrial cancer at age ≤50 yrs

- Meets Revised Bethesda Guidelines:
  Patient has a personal history of CRC AND meets one of the following:
  • Patient diagnosed at age ≤50 yrs
  • Presence of synchronous or metachronous Lynch syndrome-associated cancers, regardless of age
  • Patient diagnosed at age ≤60 yrs with a CRC that demonstrates MSI-high histology (tumour-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern)
  • One or more first-degree relatives with a Lynch syndrome-associated cancer, with one of the cancers being diagnosed at age ≤50 yr
  • Two or more first- or second-degree relatives with Lynch syndrome-associated cancers, regardless of age

- Meets Amsterdam Criteria:
  Patient and at least two close relatives who all have or have had a cancer associated with Lynch syndrome (CRC, endometrial, small bowel, ureter or renal pelvis) AND all of the following criteria must be met:
  • One must be a first-degree relative of the other two;
  • At least two successive generations must be affected;

- At least one of the cancers should be diagnosed at age ≤50 yrs;
- Familial adenomatous polyposis (FAP) should be excluded

- Unaffected patient with a close relative who meets any of the above criteria
  - Testing unaffected individuals when no affected family member is available should be considered; significant limitations of interpreting test results should be discussed

For Adenomatous Polyposis (APC and MUTYH) genetic testing

- Family history of a known APC mutation or two (biallelic) MUTYH mutations
- Personal history of a total of >10 adenomas
- Personal history of a desmoid tumor

Other Polyposis Syndrome

- Personal or family history of
  - multiple GI hamartomatous polyps or serrated polyps
  - PJS (STK11) and JPS (BMPR1A and SMAD4) mutation

Alternatively, a set of more inclusive genetic testing criteria as the following could be considered. Personal and family characteristics suggestive of Hereditary Colorectal Cancer predisposition including

- **Early onset** colorectal cancer, or several adenomas ≤50 yrs old
- **Multiple primary cancers including colorectal cancer** in one individual
- >10 polyps (adenomatous, hyperplastic, hamartomatous, and/or other types of polyps) in their lifetime
- Colorectal cancer exhibiting microsatellite instability or lack of immunostaining for a mismatch repair protein in tumour
- Several blood relatives affected with related cancers (listed in table e.g colon, uterine, ovarian, and/or stomach cancer), spanning **multiple generations**
- Pattern of previously mentioned hereditary cancer syndromes i.e Lynch Syndrome, FAP, MAP, Cowden Syndrome, Hereditary Diffuse Gastric Syndrome, Li-Fraumeni Syndrome, PJS, JPS
- **Prior genetic testing** performed due to family history suggestive of hereditary cancer predisposition, however **all results were negative**

Genes associated with Hereditary CRC are listed in Table 1 and 2 according to cancer risk level and cancer types that they predispose respectively. Cancer risk varies according to the gene that is being mutated and the risk attributable to the various genes can be classified into high and moderate risk genes. Generally, the high-risk genes confer more than 4 folds lifetime cancer risk to individuals who are carriers of the gene mutation; moderate-risk genes between 2-4 folds lifetime cancer risk; and, low-risk genes up to 2 folds lifetime cancer risk as compared to the normal population.
Most of the mutation of these cancer susceptibility genes are inherited autosomal dominantly. That is, offspring has a 50% probability of inheriting the mutation from the affected parent (paternal or maternal).

As mentioned earlier, most of the Hereditary CRC cases are due to germline mutation of the Lynch genes, MLH1, MSH2, MSH6 and PMS2 that codes for DNA mismatch repair (MMR) proteins

(Aaltonen et al, 2007), as well as EPCAM which lie up-stream of MSH2 gene. Large deletion of EPCAM could lead to epigenetic silencing of MSH2 and consequently, Lynch syndrome (Kempers et al, 2011). Of the Lynch syndrome genes, MSH2, followed by MLH1 are most frequently mutated, of which MSH2 is the most penetrant (Bonadona et al, 2011). Lynch syndrome also known as HNPCC lacks the classical early onset presentation of the numerous polyps in FAP individuals.

FAP (including AFAP) is due to germline mutation of the APC gene. Classical FAP is characterised by early presentation of ≥100 adenomatous polyps in affected individuals (Galiatsatos and Foulkes, 2006) whereas in AFAP has later presentation of these polyps and in fewer numbers (Galiatsatos and Foulkes, 2006; Half et al, 2009). The cancer risk level and associated malignancies associated with APC mutation are depicted in Table 1 and 2 respectively.

MUTYH is the other high risk gene that predisposes an individual to AFAP and CRC (Al-Tassan et al, 2002; Jones et al 2002; Theodoratou et al, 2010). MUTYH-Associated Polyposis (MAP) is an autosomal recessive hereditary syndrome and individuals with MAP have presentation of adenomatous polyps later and in fewer numbers as compared to FAP, similar to AFAP.

The other high risk genes implicated in Hereditary CRC are: JPS, BMPR1A and SMAD4 genes; PJS, STK11; Cowden Syndrome, PTEN; Hereditary Diffuse Gastric Cancer Syndrome, CDH1; Li-Fraumeni, Tp53 .

Finally, ATM, AXIN2, and CHEK2 are the newer low risk genes implicated in Hereditary CRC.

Table 1.

Risk Level	Genes	Level of lifetime risk compared to general population's
High	APC, MUTYH (Biallelic), MLH1, MSH2, MSH6, EPCAM, BMPR1A, SMAD4, STK11, PMS2, PTEN, CDH1, TP53	>4 fold, generally >50%
Low	ATM, AXIN2, CHEK2	Yet to be determined, generally up to 20%

Table 2.

Genes	Associated Malignancies
APC	Colorectal, Duodenal or periampullary, Gastric, Thyroid, Pancreatic, Brain, Liver
MUTYH (Biallelic)	Colorectal, Duodenal, Endometrial
MLH1	Colorectal, Endometrial, Ovarian, Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
MSH2	Colorectal, Endometrial, Ovarian, Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
MSH6	Colorectal, Endometrial, Ovarian, Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms

PMS2	Colorectal, Endometrial, Ovarian, Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
EPCAM	Colorectal, Endometrial, Ovarian, Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
BMPR1A	Colorectal, Gastric (if gastric polyps)
SMAD4	Colorectal, Gastric (if gastric polyps)
STK11	Colorectal, Female Breast, Pancreatic, Gastric, Ovarian tumours, Lung, Small intestine, Cervical, Endometrial, Testicular tumours
PTEN	Female Breast, Thyroid, Endometrial, Colorectal, Renal, Melanoma
CDH1	Diffuse gastric cancer, Female Breast, Colorectal
TP53	Female Breast, Soft tissue sarcoma, Osteosarcoma, Brain, Hematologic malignancies, Adrenocortical carcinoma Overall risk for cancer: nearly 100% in females, 73% in males
ATM	Female Breast, Colorectal, Pancreatic
AXIN2	Colorectal
CHEK2	Female Breast, Male Breast, Colorectal, Prostate, Thyroid, Endometrial (serous), Ovarian

There are many commercial genetic tests for detecting genes associated with hereditary cancer syndromes. They mostly use Next Generation Sequencing to detect Single Nucleotide Variants (SNVs) and small insertions and deletions (Indels) concurrently with array Comparative Genomic Hybridization or Multiplex Ligation-dependent Probe Amplification for large gene rearrangement analysis of single or multiple genes. The latter concurrent sequencing of multiple genes is often more time- and cost-efficient than stepwise single gene testing of suspicious hereditary cancer genes.

In the most recent National Comprehensive Cancer Network (NCCN) guideline for Hereditary Breast and Ovarian Cancer (2015), the followings regarding multigene panel testing are mentioned

- “Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, than multi-gene testing, may be more efficient and/or cost-effective.
- There is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.”

However, care should be exercised on the choice of laboratory offering the test, methodology and composition of the multigene panel. The same guideline highlighted that there are no clear strategies for risk management of carriers of moderate risk mutations, and the multifactorial cancer risks associated with these carriers due to gene-to-gene or gene-and –environment interactions, make it a challenge assigning cancer risk to relatives of mutation carrier.

Moreover, increased variants of unknown significance (VUS) should be expected from the use of multigene panels making it crucial to select a test provider who would adequately address the VUS in the test reports and promptly inform clinicians and patients whenever such VUSs are reclassified as harmful mutations.

Pre- and Post-Cancer Genetic test counselling are highly recommended for clinicians intending to offer Hereditary Cancer Syndrome genetic test.

Currently, the NCCN has published clinical and practice guidelines on Genetic/Familial High-Risk Assessment for Hereditary Colorectal Cancer (Table 3).

Table 3.

Version	Guideline	Genes which Management guideline specifically address
V2, 2014	NCCN Genetic/Familial High-Risk Assessment: Colon	APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM

Resources for Clinicians

National Comprehensive Cancer Network – Guidelines
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

American Society of Clinical Oncology
http://www.asco.org/

National Cancer Institute
www.cancer.gov
http://www.cancer.gov/cancertopics/pdq/genetics

Vanderbilt-Ingram Cancer Center
http://www.mycancergenome.org/

Cancer Index
http://www.cancerindex.org/

Drugs.com
http://www.drugs.com/

My Cancer Genome
http://www.mycancergenome.org/

The Cancer Genome Atlas
http://cancergenome.nih.gov/

Resources for Patients

National Cancer Institute, Cancer Topics
http://www.cancer.gov/cancertopics

Information from ASCO on Cancer for Patients
http://www.cancer.net/
http://www.cancer.net/navigating-cancer-care/cancer-basics/genetics/hereditary-cancer-related-syndromes

National Cancer Institute
www.cancer.gov

Cancer Research UK
http://www.cancerresearchuk.org/

Online Glossary on Genetics

National Institutes of Health, Genetics Home Reference (Information on Chromosomes, Genes etc.)
http://ghr.nlm.nih.gov/

National Cancer Institute
http://www.cancer.gov/cancertopics/genetics

Wellcome Trust Sanger Institute, yourgenome.org
http://www.yourgenome.org/glossary/

Your Genome Glossary
http://www.yourgenome.org/glossary/

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NCCN (2014) NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Colorectal V2

NCCN (2015) NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Breast and Ovarian V1

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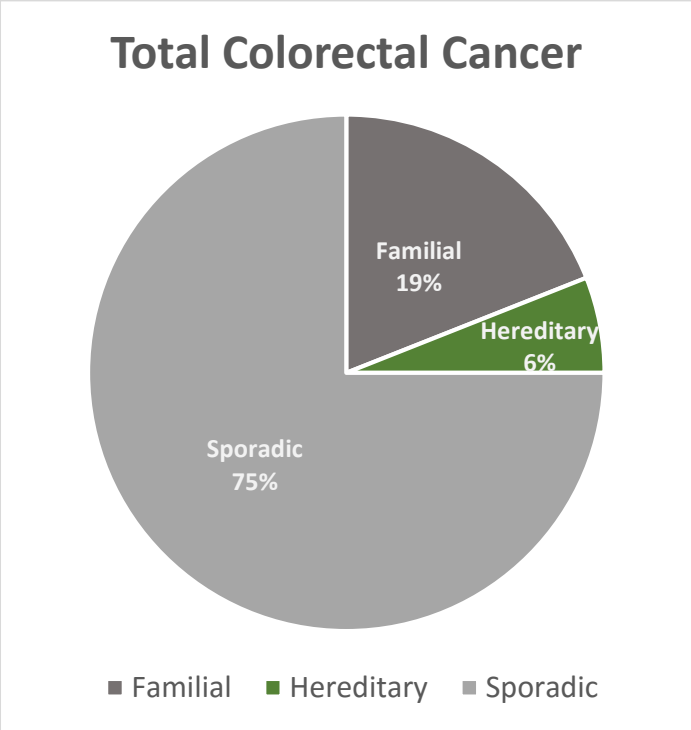

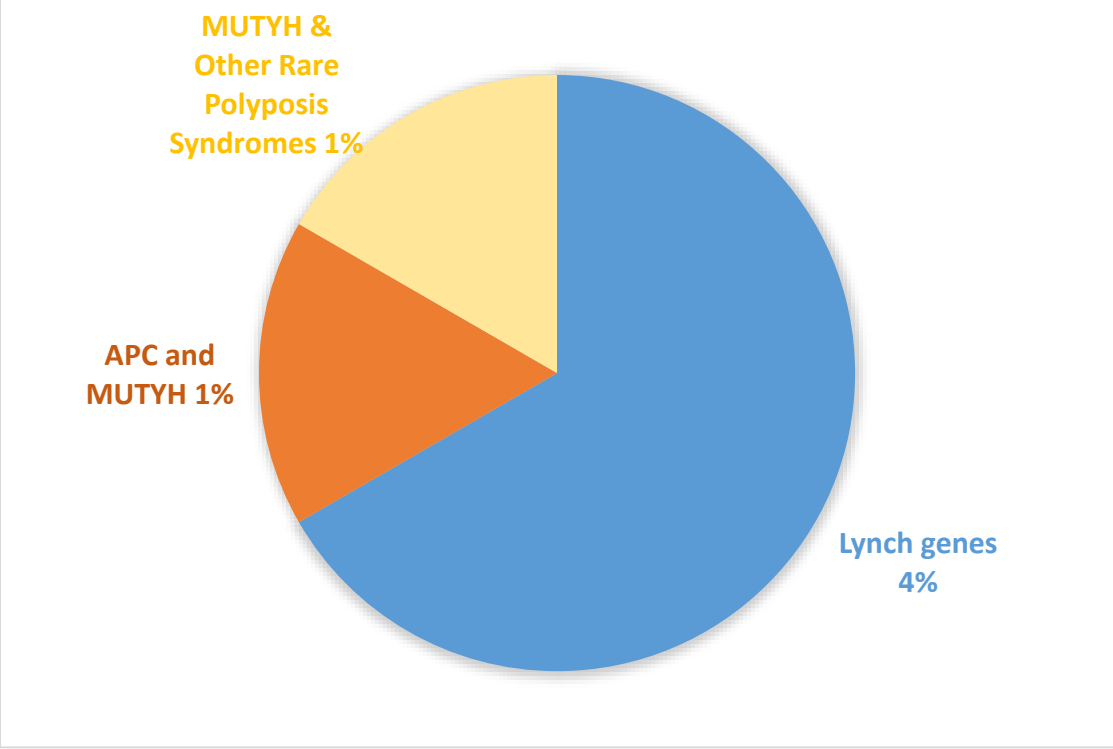

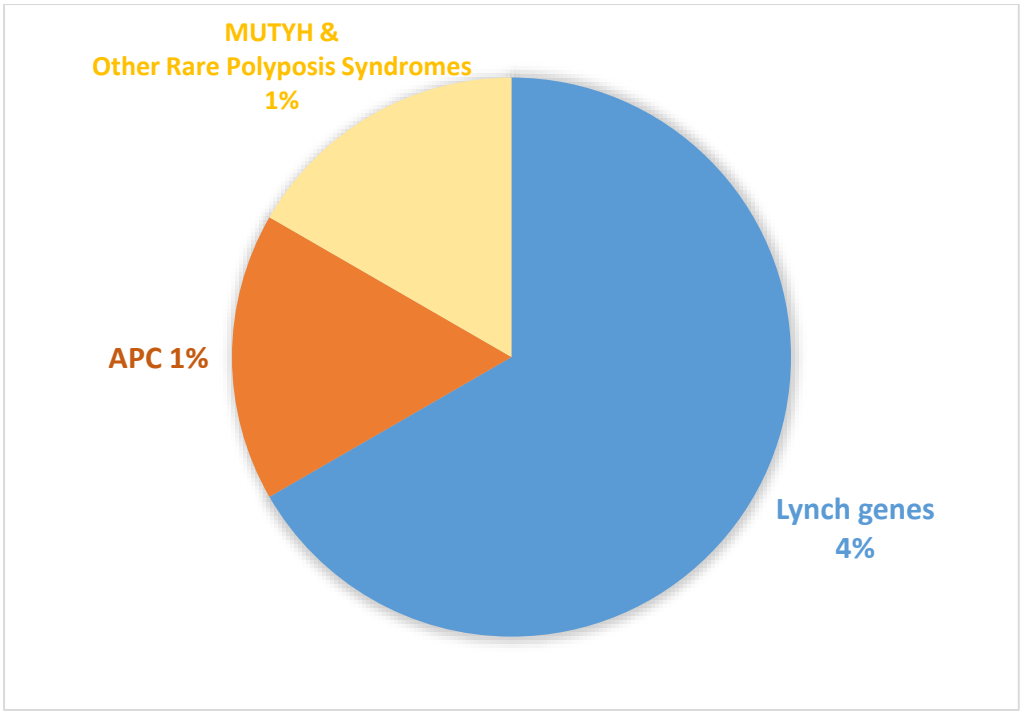
MUTYH &
Other Rare Polyposis Syndromes
1%
APC 1%
Lynch genes
4%