

Hereditary Cancer Syndrome and Genetic Testing

Tests available

- Comprehensive Multigene Panel for common Hereditary Cancer Syndromes
- Specific Hereditary Cancer Syndrome single gene and Multigene Panel tests listed in the main Cancer Genetics Menu

Contact Asia Genomics for a copy of a Genetic Test Brochure

Cancer is a disorder of the genome and mutations are required for development of all cancers. The majority of cancers occur sporadically and up to 10% of cancers are inherited.

Hereditary Cancer Syndrome is an inherited predisposition to a syndrome with specific pattern of tumour types, characterised by early onset of tumour development and presentation of multiple primary tumours in an affected individual. The multiple primary tumours in the latter share the same causative genetic mutation (Allgayer et al, 2009).

Individuals with mutations in the Hereditary Cancer Susceptibility gene has increased risk for cancer types associated with the Hereditary Cancer Syndrome. This risk varies according to the gene that is being mutated. Cancer risk attributable to the various genes can be classified into high, moderate and low risk genes (Table 1).

Table 1.

Risk classification of Gene	Level of lifetime risk compared to general population's
High Risk	>4 fold, generally >50%
Moderate Risk	2-4 folds, generally between 20-50%
Low Risk	Yet to be determined, generally up to 20%

High risk genes increase lifetime cancer risk by >4 folds or >50% compared to the general population. Moderate risk genes to between 2-4 folds or 20-50% risk compared to the general population. Low risk genes up to 20% risk compared to the general 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) (figure 1).

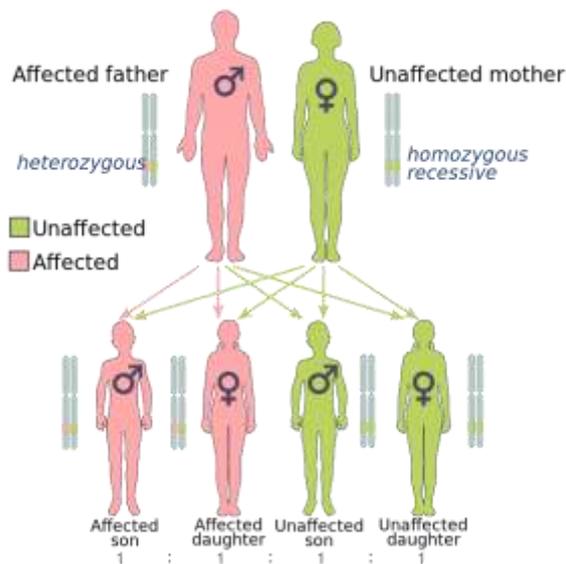


Figure 1: Autosomal dominant transmission of mutation from an affected parent to offspring. Offspring have 50% chance of inheriting the mutation from affected parent.

However, biallelic mutations of susceptibility genes can occur, though rare and are associated with extremely rare autosomal recessive syndromes (Table 2).

Table 2.

Gene	Autosomal Recessive Disorders
ATM	Ataxia-Telangiectasia
EPCAM, MLH1, MLH2, MSH6, PMS2	Constitutional mismatch repair deficiency syndrome
BRCA, BRIP1, FANCC, PALB2, RAD51C, XRCC2	Fanconi Anemia
MUTYH	MUTYH-associated polyposis (MAP)
NBN	Nijmegen breakage syndrome

According to the National Cancer Institute, the features of a person's personal and family medical history that suggest a hereditary cancer syndrome include the following (NCI, 2013)

- ✓ Cancer diagnosed at young age
- ✓ Multiple cancer types in the affected individual
- ✓ Cancer in both organs in paired organs i.e. bilateral breast cancer
- ✓ Same cancer type in multiple blood relatives
- ✓ Unusual cancers i.e. Male breast cancer
- ✓ Presence of birth defects i.e. benign skin growth, skeletal abnormalities known to be associated with inherited cancer syndromes
- ✓ Member of an ethnic group known to have increased risk for hereditary cancer syndrome i.e. BRCA mutation in Hereditary breast and ovarian cancer in Ashkenazi Jewish

Table 3: Types of Hereditary Cancer Syndromes, associated genes and malignancies adapted from Schrader et al (2014).

Hereditary Cancer Syndrome	Component Malignancies	Genes
Hereditary Breast Cancer Syndrome		
<ul style="list-style-type: none"> Hereditary Breast and Ovarian Cancer Syndrome 	Breast, Ovarian cancers Prostate, Pancreatic cancers ,melanoma, Fanconi anemia (BRCA2) in biallelic carriers, Medulloblastoma	BRCA1 BRCA2 BRCA2
<ul style="list-style-type: none"> Partner and localizer of BRCA2 	As above for BRCA2	PALB2
<ul style="list-style-type: none"> BRCA1-interacting protein 1 	As above for BRCA2; Fanconi Anemia (BRIP1) in biallelic carriers	BRIP1
<ul style="list-style-type: none"> Li Fraumeni Syndrome 	Soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumour, adrenocortical carcinoma, leukemia, or lung bronchoalveolar cancer	Tp53
<ul style="list-style-type: none"> Cowden Syndrome 	Breast, thyroid cancers, Lhermitte-Duclos disease, other cancers	PTEN KLLN SDHB SDHD
<ul style="list-style-type: none"> Bannayan-Riley-Ruvalcaba Syndrome 	Breast cancer meningioma, thyroid follicular cell tumours	PTEN
<ul style="list-style-type: none"> Ataxia telangiectasia 	Leukemia, lymphoma, ovarian, gastric cancers, brain tumours, thyroid, parotid, colon cancers, other cancers	ATM
Hereditary Gastrointestinal Malignancies		
<ul style="list-style-type: none"> Lynch Syndrome or Hereditary nonpolyposis colon cancer 	Colon, endometrial cancers; gastric, hepatobiliary, ovarian, pancreatic renal pelvis, small bowel, and ureteral cancers	MLH1 MSH2 EPCAM MSH6 PMS2
<ul style="list-style-type: none"> Familial adenomatous polyposis, including attenuated Familial adenomatous polyposis 	Colon, gastric, duodenal, ampullary cancers	APC
<ul style="list-style-type: none"> MUTYH-associated polyposis 	Colon, duodenal, ovarian, bladder cancers	MUTYH
<ul style="list-style-type: none"> Hereditary diffuse gastric cancer 	Stomach cancers, lobular breast carcinomas, colon cancer	CDH1
<ul style="list-style-type: none"> Juvenile Polyposis 	Gastrointestinal, pancreatic cancers	SMAD4 BMPR1A
<ul style="list-style-type: none"> Peutz-Jeghers Syndrome 	Colon, small bowel, breast, ovarian, pancreatic cancers	STK11
<ul style="list-style-type: none"> Hereditary mixed polyposis syndrome 	Colon cancer	GREM1
<ul style="list-style-type: none"> Hereditary pancreatic cancer 	Pancreatic, breast and ovarian cancers	BRCA2 PALB2
<ul style="list-style-type: none"> Hereditary melanoma pancreatic cancer Syndrome 	Pancreatic cancer, melanoma	CDKN2A
<ul style="list-style-type: none"> Hereditary pancreatitis 	Pancreatic cancer	PRSS1 SPINK1 CFTR c-KIT PDGFRA

<ul style="list-style-type: none"> Familial gastrointestinal stromal tumour 	Gastrointestinal stromal tumours	c-KIT PDGFRA
<ul style="list-style-type: none"> Oligodontia-colorectal cancer syndrome 	Colon cancer	AXIN2

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 Breast and Ovarian Cancer, as well as Hereditary Colorectal Cancer (Table 4).

Table 4.

Version	Guideline	Genes which Management guideline specifically address
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V1, 2015	NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian	BRCA1 and 2, Tp53, PTEN, ATM, CDH1, CHEK2, PALB2, STK11, MLH1, MSH2, MSH6, PMS2, EPCAM
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/>

Cell Signaling pathways

<http://www.cellsignal.com/common/content/content.jsp?id=science-pathways>

National Society of Genetic Counselors.

www.nsgc.org

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

National Cancer Institute, Patient and Caregiver Resources

<http://www.nccn.org/patients/default.aspx>

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/>

References

Allgayer, H., Rehder, H., and Fulda, S. (2009). Hereditary Tumours, from genes to clinical consequences. Germany. Wiley.

National Cancer Institute (2013) Genetic Testing for Hereditary Cancer Syndromes. Retrieved on 31 Oct 2014, from <http://www.cancer.gov/cancertopics/factsheet/Risk/genetic-testing>

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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