Hereditary Breast and Ovarian Cancer (HBOC)

Tests available

- BRCA 1 & 2
- HBOC High Risk genes
- HBOC Comprehensive Multigene Panel

Contact Asia Genomics for a copy of a Genetic Test Brochure

Breast cancer is the most common non-cutaneous cancer in women. The lifetime risk of breast cancer in North America is 12% (SEER, 2009) and relatively the same in the United Kingdom (UK) (Hodgson et al, 2014). It is the leading cause of cancer death in the North America after lung cancer (American Cancer Society, 2015). In Singapore, it is the most commonly diagnosed cancer among women (Singapore Cancer Registry, 2015). Like most cancers, the majority of breast cancer occur sporadically and up to 10% have a hereditary basis (figure 1).

The lifetime risk of ovarian cancer, on the other hand, is about 1.5% in North America and the UK (Hodgson et al, 2014). In Singapore, it is fifth most common malignancy in women (Singapore Cancer Registry, 2015) and generally associated with high mortality rate since most ovarian cancers are diagnosed at late staged. Epithelial ovarian cancer is the most common form of ovarian cancer and up to 25% may have a hereditary basis (figure 2) (Walsh et al, 2011; Pennington et al, 2014).

Figure 1.

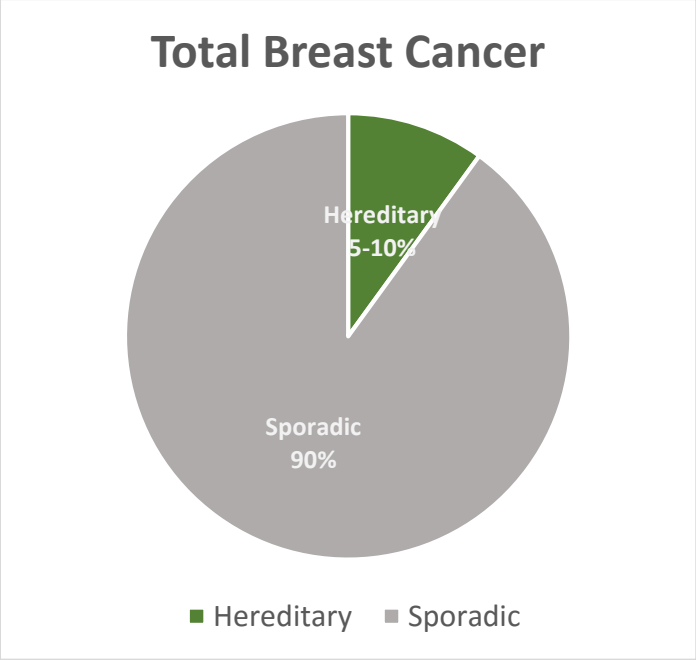
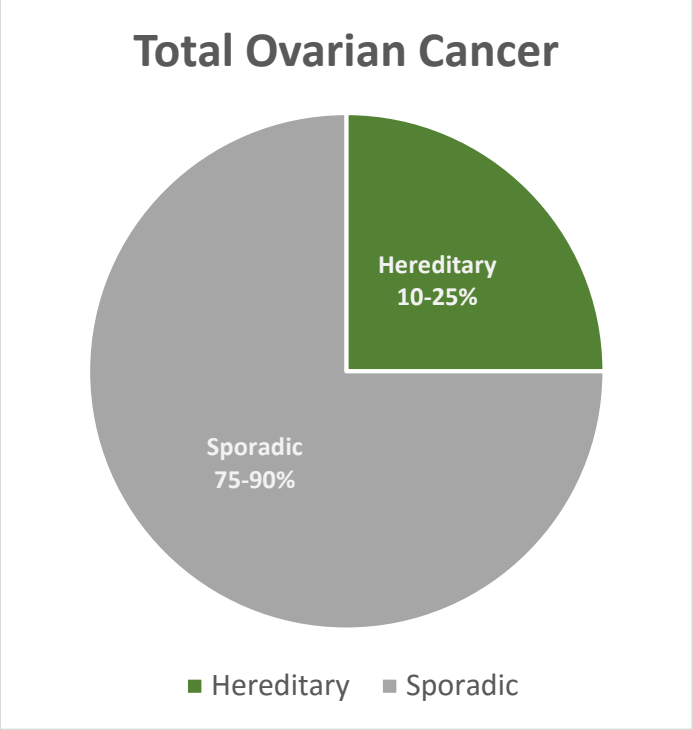


Figure 2.



According to the NCCN guideline (2014), personal and family characteristics suggestive of Hereditary Breast and Ovarian Cancer predisposition include the following

- Early onset Breast Cancer, age 45 years or younger at first diagnosis
- Bilateral tumours i.e. bilateral breast cancer in an affected individual
- Triple negative breast cancer
- Multiple primary cancers in an affected individual
- Many blood relatives affected by related cancers (i.e. Breast, epithelial ovarian cancer, pancreatic and prostate cancer) across multiple generations
- Uncommon cancer i.e. Male breast cancer
- A pattern of cancer typical of known cancer predisposition syndrome

Current findings state that up to 50% of hereditary breast cancers could be attributed to BRCA1 and BRCA2 mutations, with the remaining due to other genes (figure 3) (The Cancer Genome Atlas Network, 2012).

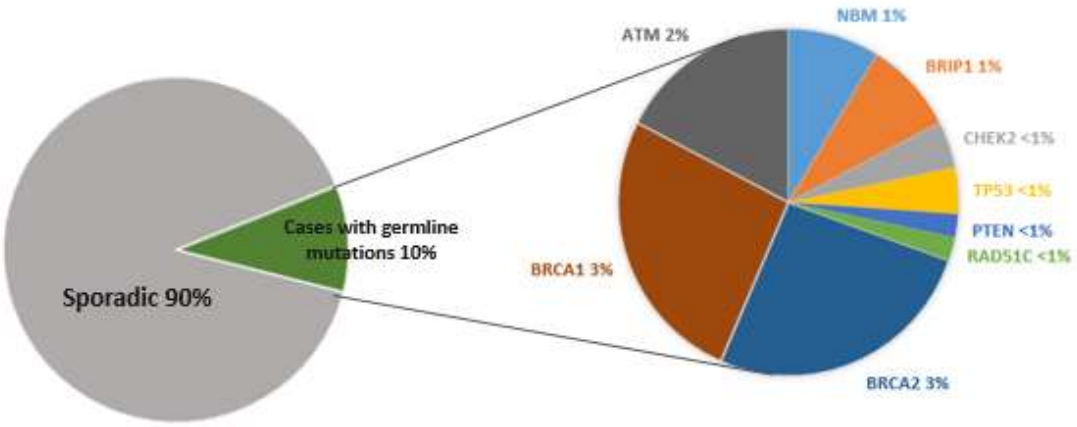


Figure 3.

Exome analysis of total breast cancer cases (n=507) showed that approximated 10% are hereditary with various germline mutations of genes. (From Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61-70)

According to the NCCN guidelines (2014), the other non-BRCA genes implicated in HBOC are CDH1, PTEN, TP53, STK11 (known to be associated with Hereditary Diffused Gastric Cancer Syndrome, Cowden Syndrome, Li-Fraumeni and Peutz-Jeghers Syndrome respectively) and seventeen other moderate and low risk genes (Table 1.)

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).

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.

In addition, these 23 genes may each predispose a carrier to cancer types beyond HBOC. Their associated cancer type risks are listed in table 2 below.

Table 1.

Risk Level	Genes	Level of lifetime risk compared to general population's
High	BRCA1, BRCA2, CDH1, PTEN, TP53, STK11	>4 fold, generally >50%
Moderate	MLH1, MSH2, MSH6, MUTYH, PMS2, ATM, CHEK1, CHEK2, MRE11A, PALB2, RAD50	2-4 folds, generally between 20-50%
Low	BARD1, BRIP1, NBN, RAD51B, RAD51C, RAD51D	Yet to be determined, generally up to 20%

Table 2.

Genes	Associated Malignancies
BRCA1	Female Breast, Ovarian, Prostate , Male Breast, Pancreatic, Fallopian tube, Primary peritoneal, Endometrial (serous)

BRCA2	Female Breast, Ovarian, Prostate, Male Breast, Pancreatic, Melanoma, Fallopian tube, Primary peritoneal, Endometrial (serous)
CDH1	Female Breast, Diffuse gastric cancer, Colon
PTEN	Female Breast, Thyroid, Endometrial adenocarinoma, Colon, Renal, Melanoma Uterine leiomyoma
TP53	Female Breast, Soft tissue sarcoma, Osteosarcoma, Brain, Hematologic malignancies, Adrenocortical carcinoma Overall risk for cancer: nearly 100% in females, 73% in males
STK11	Female Breast, (Non-epithelial) Ovarian tumours, Colorectal, Pancreatic, Gastric , Lung, Small intestine, Cervical, Endometrial, Testicular tumours
ATM	Female Breast, Colon, Pancreatic
CHEK2	Female Breast, Male Breast, Colon, Prostate, Thyroid, Endometrial, Ovarian
MRE11A	Breast, possibly Ovarian, Ataxia-telangiectasia-like disorder
PALB2	Female Breast, Male Breast, Pancreatic, Ovarian
RAD50	Breast, possibly Ovarian, biallelic mutation results in Nijmegen breakage syndrome-like disorder
MLH1	Ovarian, Colorectal, Endometrial, Gastric, Pancreatic, Billary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
MSH2	Ovarian, Colorectal, Endometrial, Gastric, Pancreatic, Billary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
MSH6	Ovarian, Colorectal, Endometrial, Gastric, Pancreatic, Billary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
MUTYH	Breast, Colorectal , billallelic mutation results in MUTYH-associated polyposis, MAP
PMS2	Ovarian, Colorectal, Endometrial, Gastric, Pancreatic, Billary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms
BARD1	Female Breast, Ovarian
BRIP1	Female Breast, Ovarian
NBN	Female Breast, Melanoma, Non-Hodgkin lymphoma, maybe ovarian
RAD51C	Female Breast, Ovarian
RAD51D	Female Breast, 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 Breast and Ovarian Cancer (Table 3).

Table 3.

Version	Guideline	Genes which Management guideline specifically address
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

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/

References

American Cancer Society. (2015). Cancer Facts and Figures 2015. Atlanta, Ga: American Cancer Society. Available online. Last accessed January 7, 2015

Cancer Genome Atlas Network. (2012). Comprehensive molecular portraits of human breast tumours. Nature (490), 61-70.

Hodgson, S.V., Foulkes, C.E. and Maher, E.R. (2014). A practical guide to human cancer genetics. London: Springer-Verlag.

National Comprehensive Cancer Network (2014) NCCN clinical guideline for Genetic/Familial High-Risk Assessment: Breast and Ovarian v2.

National Comprehensive Cancer Network (2015) NCCN clinical guideline for Genetic/Familial High-Risk Assessment: Breast and Ovarian v1.

Pennington, K.P., et al. (2014). Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res, 20(3): p. 764-75.

Singapore Cancer Registry. (2015). Annual Registry Report, Trends in Cancer Incidence in Singapore, 2009-2013. Singapore: National Registry of Diseases Office.

Walsh, T., et al. (2011). Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A, 108(44): p. 18032-7.

Last updated 08APR2015