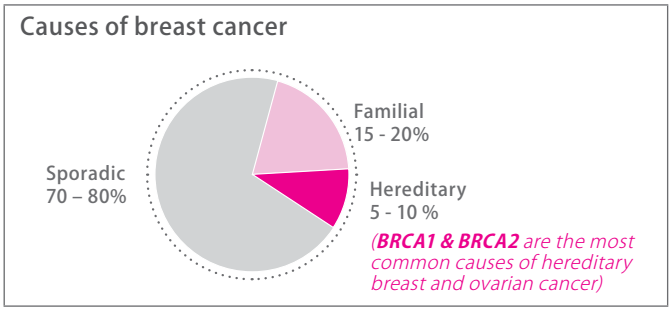
THE PATHCARE NEWS

INTERNATIONAL GENETIC TESTING FOR HEREDITARY BREAST AND OVARIAN CANCER

The majority of breast and ovarian cancers are sporadic; however, approximately **5–10%** of breast cancers and **10–15%** of ovarian cancers are **hereditary** and passed down through generations.



Hallmarks of hereditary breast/ovarian cancer
• Breast cancer diagnosed **< 50 years**
• Ovarian cancer diagnosed **< 60 years**
• Bilateral breast cancer
• Male breast cancer
• Triple negative breast cancer
• High risk ancestry (especially Ashkenazi Jewish)
• Multiple individuals with breast, ovarian, pancreatic, prostate cancer, and/or melanoma in close relatives **< 50 years**

There are many hereditary cancer syndromes associated with breast and ovarian cancer; one of the most common syndromes is called Hereditary Breast and Ovarian Cancer Syndrome (HBOCS) which is caused by pathogenic variants (mutations) in two genes, *BRCA1* and *BRCA2*. PathCare is proud to offer both in-house and international send away genetic testing for hereditary breast and ovarian cancer.

PathCare in-house *BRCA1* and *BRCA2* Genetic Testing

1. *BRCA1* & *BRCA2* Comprehensive Testing

This comprehensive test sequences both the *BRCA1* and *BRCA2* genes, and includes deletion/duplication analysis. *BRCA1/2* variants account for 50-60% of hereditary breast cancer cases. Therefore, this test is a good starting point to direct management decisions. The test is designed for affected individuals with an activated medical aid oncology benefit. Confirmation of cover is required prior to testing.

2. *BRCA1* & *BRCA2* Founder Variant Testing

There are specific pathogenic variants in the *BRCA1* and *BRCA2* genes that have been shown to be particularly prevalent in the Ashkenazi Jewish and Afrikaner populations. Founder variant testing is a first tier, cost-effective option for patients that belong to these population groups and for whom other testing is unaffordable.

A total of 6 founder variants in the *BRCA1* and *BRCA2* genes are tested for in 2 separate tests (these tests are billed separately):

a. 3 Afrikaner founder variants
b. 3 Ashkenazi Jewish founder variants

Over 3000 likely pathogenic or pathogenic variants have been described in *BRCA1* and over 5000 in *BRCA2* (Clinvar[+]). Therefore, **a negative result for a founder variant test does NOT exclude a *BRCA1* or a *BRCA2* variant.** If your patient tests negative, more comprehensive testing is strongly recommended, particularly in cases where there is a strong suspicion of a genetic predisposition. Comprehensive testing may also be used to exclude a *BRCA1/BRCA2* variant for treatment purposes.

[+] (Clinvar https://www.ncbi.nlm.nih.gov/clinvar/)

3. *BRCA* Family Variant Testing

If a *BRCA1/2* variant has already been identified in a patient's family, targeted testing for this known familial variant can be offered to the patient and other at-risk family members. A copy of the report detailing the familial *BRCA1/2* pathogenic variant needs to be attached to the request form. This type of testing is often predictive testing (i.e., testing of an unaffected individual), therefore genetic counselling is highly recommended.

As the running costs of genetic tests depend directly on the referral numbers, it is difficult to compete with international laboratories in terms of cost. For this reason, we have looked at international send away options to make genetic testing accessible to patients and families, as referred by their managing clinician or genetic counsellor.

INVITAE - International send away service

PathCare offers a referral service to Invitae Laboratory in the USA. Invitae offers an extensive genetic test menu over a broad range of clinical areas, including hereditary cancer:
https:// www.invitae.com/en/physician/category/CAT000015/

Invitae offers testing via single-gene or multi-gene panels at a fixed patient-pay price, with the additional benefits of re-requisitioning a sample for additional genes at no extra cost, and free-of-charge family variant testing to blood relatives, if requested within 150 days of the initial patient's report (the PathCare handling fee **will** still apply).

The cost of any Invitae hereditary cancer panel (regardless of the number of genes tested) is **299 US Dollars*** (cost in Rands is dependent on the exchange rate). As this is a patient-pay option, Invitae bills the patient directly for these tests. PathCare charges an international handling fee (**R950***) which is paid upfront when providing the sample. The turnaround time for Invitae tests is approximately 4 weeks and for the more urgent STAT panels it is 2-3 weeks.

Testing offered by Invitae includes:

1. Invitae Breast Cancer STAT Panel

This panel analyses 9 well-established genes associated with an increased risk of developing breast cancer. This panel may be requested when an accelerated turnaround time (TAT) is needed to facilitate urgent surgical and management decisions. The TAT for this panel is 5-12 calendar days (7 days on average) once the sample arrives at Invitae. One can expect a report within 3 weeks of sample collection.

This test is appropriate for breast cancer patients with upcoming cancer-related breast surgeries and/or treatment where genetic testing may inform decisions such as lumpectomy versus mastectomy, single versus double mastectomy, or use of other treatments (such as use of PARP-inhibitors or other chemotherapy treatments). If a patient tests negative for the genes analysed on this panel, their sample may be re-requisitioned for the full

19 gene Invitae Breast and Gynae panel or any other appropriate panel (within the same clinical area) at no additional charge within 150 days.

2. Invitae Breast Cancer Guidelines-based Panel

The Invitae Breast Cancer Guidelines-Based Panel analyses 11 genes that are associated with hereditary predisposition to breast cancer and for which there are medical management recommendations.

3. Invitae Breast and Gynae Guidelines-based Panel

This comprehensive panel analyses 19 genes (including *BRCA1* and *BRCA2*) associated with a significantly increased lifetime risk of hereditary breast, ovarian and other gynaecological cancers. All genes on this panel have published management guidelines.

This option is more comprehensive and is indicated when a patient's family history is suggestive of a cancer syndrome other than *BRCA*-related HBOCS.

4. Invitae Family Variant Testing

When a family member has been tested through Invitae and a pathogenic/likely pathogenic variant has been identified, free-of-charge targeted family variant testing is available to family members of this patient within 150 days of the initial patient's report. The PathCare International referral service handling & courier fee (R950) will apply to family testing.

The original report from Invitae (including the RQ number) will need to accompany these samples. Adequate genetic counselling is also recommended, as this testing may be offered to at-risk unaffected family members.

Genetic Counselling

It is internationally recognised and strongly recommended that genetic testing be offered in the context of appropriate pre- and post-test genetic counselling by a genetics professional.

PathCare does not offer a clinical genetic counselling service but is able to provide you with contact details for genetic counsellors in South Africa. Please contact our Genetics Team for a list of HPCSA-registered genetic counsellors who you can refer your patients to. We understand that there are limited genetic counselling services in South Africa, however, most genetic counsellors would be able to arrange online consultations if necessary.

Please feel free to contact our **Genetics Team** if you have any questions on:

(021) 596 3655

geneticconsult@pathcare.org

Quick Guide To Testing

(Please use for all requests.)

Laboratory	PathCare			Invitae			
Test	*BRCA1* & *BRCA2* Comprehensive testing	*BRCA1* & *BRCA2* Founder mutation testing	Known *BRCA* family variant testing	Breast Cancer STAT Panel (9 genes)	Breast Cancer Guidelines-Based Panel (11 genes)	Breast and Gyn Cancers Guidelines-Based Panel (19 genes)	Family variant testing
Description	Comprehensive testing should detect all known pathogenic and novel variants in these genes	2 separate tests Common founder variants in the SA population: a. 3 Afrikaner variants b. 3 Ashkenazi Jewish variants	Testing for a known *BRCA* variant in the family	Breast cancer genes	Breast cancer genes	Breast and gynaecological cancer genes	Testing for a known mutation in the family
When to order?	Patients who do not fall into a founder population group. Patient whose founder variant test is negative. Patients whose medical aid will cover the cost of local testing.	These are first line tests for patients with relevant ancestry. This is NOT a comprehensive test.	Following adequate pre-test genetic counselling. Attach copy of original report from family member.	This panel is ideal for patients who require results quickly, e.g. for surgical decision making.	Patients who require more comprehensive genetic screening, or whose family history fits a genetic cancer predisposition syndrome other than HBOCS.		Following adequate pre-test genetic counselling. Attach copy of original Invitae report from family member.
Turnaround time	2 – 3 weeks	1 – 2 weeks	1 – 2 weeks	2 – 3 weeks	~ 4 weeks		~ 4 weeks
Sample type	EDTA 4ml whole blood			EDTA 4ml whole blood Buccal swab available on request *(Sample failure may occur. In rare occasions, a repeat sample may be requested)*			

** Pricing is correct and valid as of September 2023. Please contact the PathCare Genetics Team for confirmation of current prices.*