The spectrum of variants in hereditary breast cancer: Perspectives from a private diagnostic laboratory

Danielle Smith, Amber Gardiner, Petra Raimond, Ilze Uys, Janine Blanckenberg, Jaclyn Gerber, Maureen Conradie, Frieda Loubser
Molecular Laboratory, Drs Dietrich, Voigt, Mia & Partners (PathCare) Reference Laboratory, Cape Town, South Africa
Correspondence: molecular@pathcare.co.za

Introduction

Breast cancer is the most common malignancy in South African women, accounting for approximately 22% of local cancer cases, and 5-10% of these cases are considered to be hereditary. In the local context, founder variant testing may be requested as a first-line genetic test for individuals of Ashkenazi Jewish or Afrikaner ancestry. Alternatively, clinicians may request comprehensive screening of the full *BRCA1* and *BRCA2* genes, or utilise multi-gene panels that include additional relevant genes such as *PALB2, CHEK2* and *ATM.* Currently, no data is available on the detection rates of the various testing options that are available to South African clinicians and their patients. Information about the detection rates of these tests may assist managing clinicians and genetic counsellors to select the most appropriate and economical approach to testing for families with hereditary breast cancer.

Methods

A retrospective analysis was performed on the results obtained from the following tests, over a 3 year period:

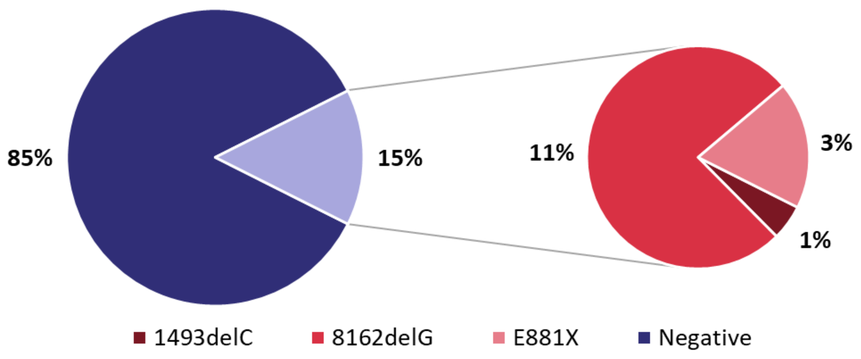
- An in-house screen for three Afrikaner founder mutations (*BRCA1* 1493delC, *BRCA1* E881X, *BRCA2* 8162delG)*
- An in-house screen for three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, *BRCA2* 6174delT)*
- An in-house next generation sequencing screen of the coding regions of the *BRCA1* and *BRCA2* genes
- International referrals to Invitae laboratory (USA) for multi-gene panel tests

Results – Founder screens

Afrikaner founder screen:

- Over the three year period, positive results were obtained in 15% of Afrikaner founder screen results (n=655).
- The most common Afrikaner founder mutation was the *BRCA2* 8162delG variant.

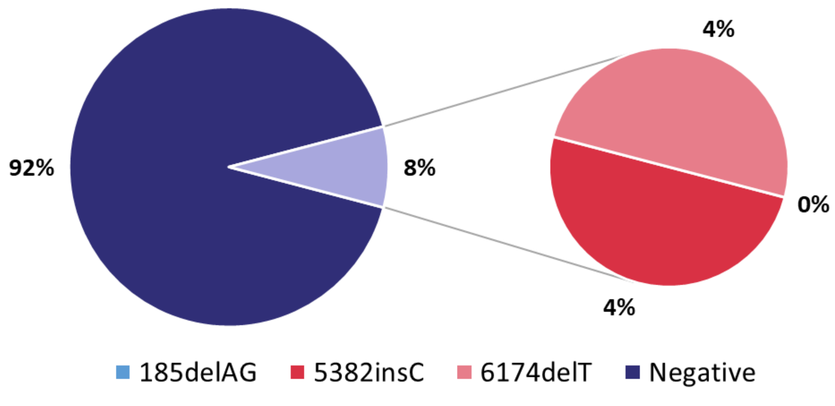
Figure 1: Afrikaner founder mutation results



Ashkenazi Jewish founder screen:

- Over the three year period, positive results were obtained in 8% of Ashkenazi Jewish founder screen results (n=49).
- The *BRCA1* 5382insC and *BRCA2* 6174delT variants were detected at equal frequencies. No individuals with the *BRCA1* 185delAG variant were identified.

Figure 2: Jewish founder mutation results



Results – *BRCA1* and *BRCA2* full screen

- Over the three year period, positive results were obtained in 7% of *BRCA1/2* full screen results (n=260).
- 65% of pathogenic variants were found in *BRCA1*.

Figure 3: BRCA Full screen results

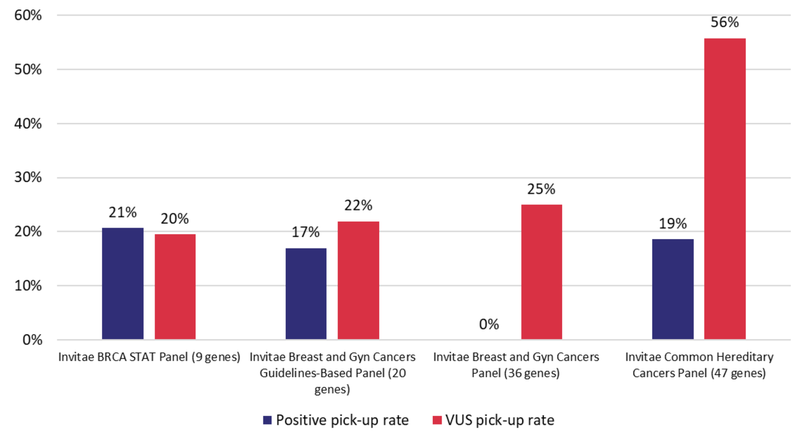
Results – Invitae referrals

Clinicians and genetic counsellors requested the following Invitae multi-gene panels:

- Invitae BRCA STAT Panel (9 genes, n=87)
- Invitae Breast and Gyn Cancers Guidelines-Based Panel (20 genes, n=383)
- Invitae Breast and Gyn Cancers Panel (36 genes, n=4)
- Invitae Common Hereditary Cancers Panel (47 genes, n=43)

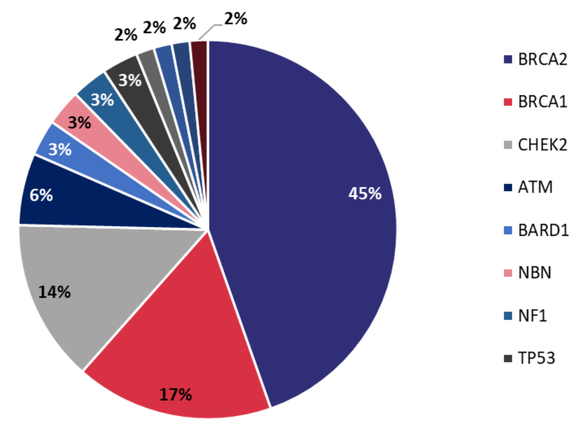
Referrals for the 9 gene BRCA STAT panel showed the highest pick-up rate (21%) and the lowest rate of variants of uncertain significance (20% VUS).
The 20 gene and 47 gene panels showed pick-up rates of 17% and 19% respectively. The 47 gene panel showed the highest VUS rate.

Figure 4: Referrals to Invitae laboratory



In these multi-gene panel results, 38% of disease-causing variants (either pathogenic or likely pathogenic variants) were detected in genes other than BRCA1/BRCA2.

Figure 5: Genes with pathogenic variants



Conclusions

These results indicate that a multi-gene approach may be the appropriate first-line testing option for suspected hereditary breast and ovarian cancer in South Africa, particularly in light of the decreasing costs of these assays.

*BRCA founder nomenclature: BRCA1 c.1374del (1493delC); BRCA1 c.2641G>T (E881X); BRCA2 c.7934del (8162delG); BRCA1 c.68_69del (185delAG); BRCA1 c.5266dup (5382insC); BRCA2 c.5946del (6174delT)