Beyond *BRCA*: Genetic testing for gynaecological cancers in South Africa

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Background. Hereditary cancer syndromes, caused by pathogenic variants in specific genes, substantially increase an individual's risk for cancer, and are estimated to cause 10% of all uterine cancers and 20% of all ovarian cancers. However, these data are primarily based on high-income countries, and to date there are no published data on the known pathogenic variants or testing of cancer predisposition genes associated with gynaecological cancers in South Africa.

Objectives. To investigate the uptake and type of molecular testing performed on patients with a suspected hereditary cancer syndrome associated with gynaecological cancer, and to assess whether patient characteristics impacted the detection of pathogenic variants.

Methods. A retrospective file review was performed for patients with a confirmed diagnosis or family history of gynaecological cancer, seen by a single clinical genetics centre in Johannesburg between 2003 and 2023. Demographic information, family history and medical information were recorded and analysed.

Results. A total of 104 records were included in analysis. The majority (73/104, 70.2%) of patients were seen in the private healthcare system, of whom most (41%) were of European ancestry. Of the remaining 31 public healthcare patients, the majority were of indigenous African ancestry (42%). Most (78/104, 75.0%) underwent diagnostic genetic testing. Of these, 25 (32.1%) were positive for pathogenic variants, 41 (52.6%) were negative and 12 (15.4%) returned a variant of unknown significance. Test results were significantly different between patients of European and non-European ancestry ($p<0.05$), with those of non-European ancestry 30% less likely to have a pathogenic variant detected (odds ratio 0.7, 95% confidence interval 0.22 - 2.21).

Conclusion. A disparity exists not only in genetic testing availability but also clinic attendance between the public and private healthcare systems, which likely limits the ability to diagnose hereditary cancer syndromes associated with gynaecological cancers in public healthcare hospitals.

Keywords: gynaecological oncology, hereditary cancers, genetic counselling, hereditary breast and ovarian cancer (HBOC), ovarian cancer, uterine cancer, Lynch syndrome

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Gynaecological cancers were the fourth most frequently diagnosed cancer worldwide in 2020, accounting for 15.3% of cancer deaths in women.[1] In South Africa (SA), cervical cancer is the most common gynaecological cancer, followed by uterine and ovarian cancers.[2] Where cancer of the cervix is almost entirely caused by human papilloma virus infection,[3] ~10% of uterine cancers and >20% of ovarian cancers are caused by a genetic predisposition.[4,5] The majority of heritable cancers are caused by two well-known hereditary cancer syndromes (HCSs): hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome.[6] Two less common HCSs known to cause gynaecological cancers are Peutz-Jegher syndrome and Cowden syndrome.[6] In addition, pathogenic variants (PVs) in several other genes, such as *PALB2*, *RAD51C*, *RAD51D* and *BRIP1*, are responsible for hereditary ovarian cancers.[7] Table 1 illustrates the marked increase in lifetime risk of developing various gynaecological cancers compared with the general population depending on which gene has the PV.

In developed countries, multi-gene sequencing panels have become routine in diagnosing HCSs, with the advantage of detecting PVs in multiple genes simultaneously due to phenotypic overlap.[11] Detected variants are classified according to set guidelines, such as the American College of Medical Genetics and Genomics/American Association of Molecular Pathology guidelines, as either pathogenic (P), likely pathogenic (LP), variant of unknown significance (VUS), likely benign (LB) or benign (B).[12] P and LP variants are known to be disease causing, and therefore clinically actionable and reported. B and LB variants are considered part of normal genetic diversity, and are therefore not reported. While VUSs have insufficient evidence to be classified as either pathogenic or benign, these are reported but cannot be used in clinical decision-making.[12] Before genetic testing for a HCS can be considered, a risk assessment is carried out to estimate how likely a patient is to be a carrier of a germline PV. This is in accordance with international guidelines to maximise the P/LP detection rate while minimising the cost of testing and limiting the detection of VUSs.[13-15]

The molecular diagnosis of a HCS through the detection of a P or LP variant enables potentially life-saving opportunities in treatment and prevention for affected individuals. In certain instances, prophylactic risk-reducing surgeries can be offered even before cancer develops. Personalised and more extensive cancer screening can be implemented for cancers associated with the HCS to improve the likelihood of early cancer detection and prognosis.[16] Furthermore, genetic testing can inform patient care and management, an example being poly-(adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitors, which are a well-established targeted therapy for ovarian cancer caused by PVs in *BRCA1* or *BRCA2*.[17] Lastly, by knowing their genetic

Table 1. Lifetime risk of gynaecological cancers for those with a defined genetic predisposition

Cancer type	General population risk, %	Genetic predisposition risk, %											
		BRCA1*	BRCA2*	PALB2†	RAD51C†	RAD51D†	BRIP1†	MLH1‡	MSH2‡	MSH6‡	PMS2‡	STK11§	PTEN¶
Ovarian	1.2	44	17	5	11	13	6	11	17	11	3	32.4	-
Uterine	3.1	-	-	-	-	-	-	37	49	41	3	49.6	28.2
Cervical	0.6	-	-	-	-	-	-	-	-	-	1	0.9	-

*Hereditary Breast and Ovarian Cancer syndrome.
†Hereditary ovarian cancers.
‡Lynch syndrome.
§Peutz-Jegher syndrome.
¶Cowden syndrome.
Data from Beggs *et al*;[8] Kalra *et al*.;[9] American Cancer Society.[10]

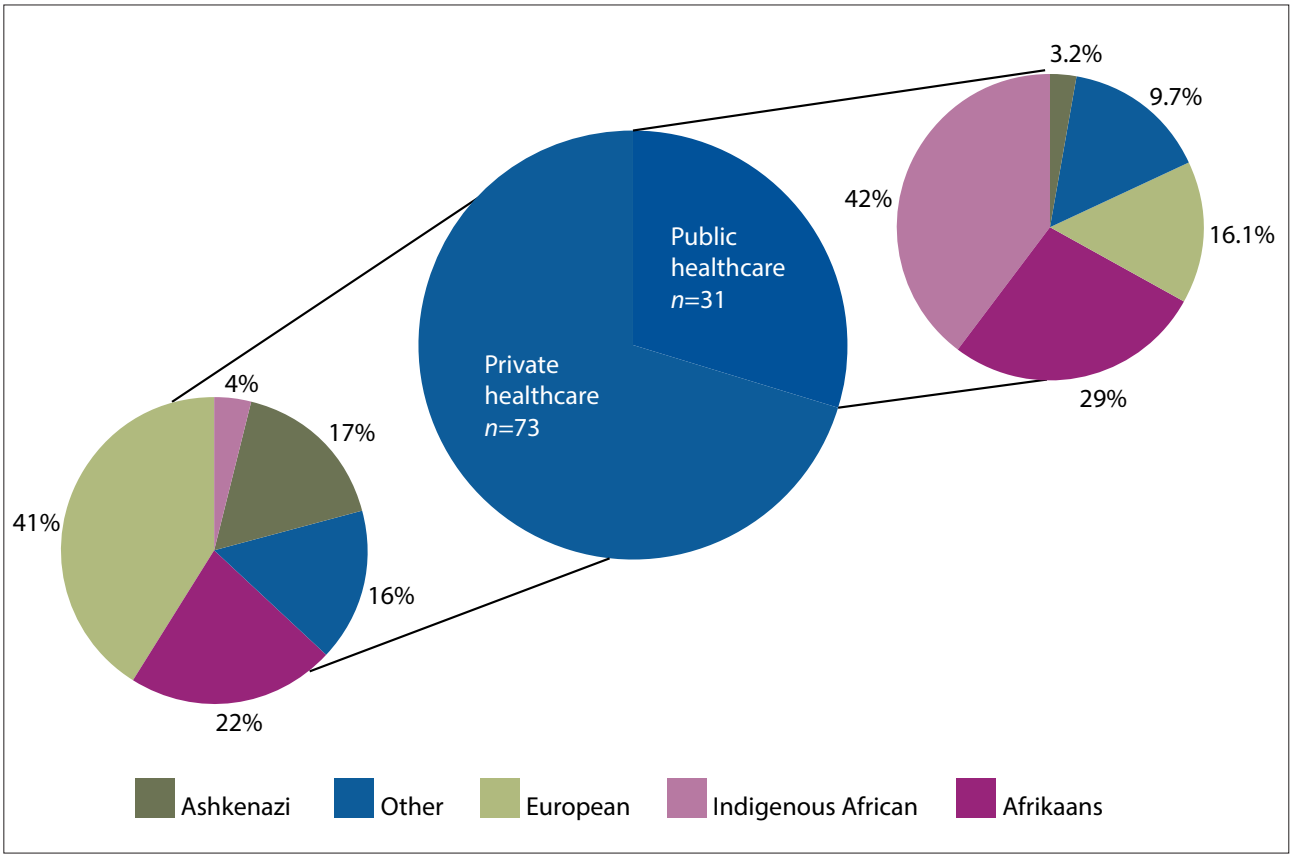

Fig. 1. Self-reported ancestry distribution among study participants in public and private healthcare settings.

status, women can make more informed lifestyle, contraceptive and reproductive choices.[9] These interventions are not limited to affected individuals but include all at-risk relatives who test positive for the disease-causing familial variant, even in the absence of cancer.[14] Familial variant testing is an expedited and less costly form of genetic testing (as opposed to a multigene panel), which either confirms or excludes the presence of the familial variant, and so does not generate VUSs. Familial variant testing for HCSs could therefore serve as an effective means of reducing cancer incidence and mortality, making this especially useful in the resource-limited context of SA.[18]

Genetic testing for HCSs in SA began in 2005, but was limited to *BRCA1* and *BRCA2* in public healthcare.[19] Only recently has genetic testing for cancers been expanded to gene panel testing, including *BRCA1* and *BRCA2* as well as *ATM*, *BARD*, *BRIP1*, *CDK12*, *CHEK2* and *PALB2*, which has led to an increased detection rate of actionable PVs.[20] Testing in public healthcare is free for citizens, subject to a means test.[21] The limitation of this panel is that only half of these genes (*BRCA1*, *BRCA2*, *BRIP1*, *PALB2*) are associated with hereditary ovarian cancers, and none of the genes causing Lynch syndrome are included. For patients in private healthcare, more comprehensive testing for HCSs has been available for much longer through private laboratories, both locally and internationally, but these often require out-of-pocket payment. International testing offers several advantages over local testing, including more comprehensive and cost-effective testing. SA studies on HCSs have mostly focused on breast cancer, producing valuable contributions to the discovery of genetic differences in various SA populations, as well as screening and testing procedures.[19,22,23] However, there is limited research into genetic testing for gynaecological cancers, detection rates and causative variants.[24] Therefore, the aim of this study was to conduct a retrospective file review of patients seen with a confirmed diagnosis or family history of gynaecological cancer by a single clinical genetics centre in Johannesburg, SA. Access to different genetic testing options and diagnostic yield were assessed.

Table 2. Patient characteristics (*N*=104)

Characteristic	*n* (%)
Sex	
Female	98 (94.2)
Male	6 (5.8)
Age at time of consultation, years	
Mean (SD), range	49.6 (14.7), 15.3 - 78.7
<18	1 (0.1)
18 - 29	9 (8.7)
30 - 39	19 (18.3)
40 - 49	20 (20.2)
50 - 59	31 (29.8)
≥60	24 (23.1)
Reason for referral	
Gynaecological cancer	35 (33.7)
Family history of gynaecological cancer	40 (38.5)
Personal and family history of gynaecological cancer	10 (9.6)
Family variant testing for HCS associated with gynaecological cancers	19 (18.3)
Population ancestry	
Indigenous African	16 (15.4)
Afrikaner	24 (23.1)
European	35 (33.7)
Ashkenazi Jewish	13 (12.5)
Other*	16 (15.4)
Healthcare sector	
Public	31 (29.8)
Private	73 (70.2)

SD = standard deviation; HCS = hereditary cancer syndrome.
*'Other' assigned when not reported (9/16, 56.3%). The remaining seven patients consisted of 2 (28.6%) of Cape Malay, 2 (28.6%) of Lebanese and 3 (42.9%) of Indian ancestry.

Methods

Patients who met the inclusion criteria between January 2003 and May 2023 were used to conduct the retrospective file review for a clinical genetics centre in Johannesburg. Patients were referred for one or more high-risk factors related to their personal and family history of cancer. High-risk factors included a diagnosis of ovarian cancer <60 years of age; high-grade serous ovarian carcinoma at any age; uterine cancer <50 years of age; individuals of any age with multiple primary tumours or bilateral disease; family history of multiple related cancers (including breast, ovarian, prostate, pancreatic, colon and uterine cancer); and personal or family history of cancer from high-risk population groups (Afrikaner or Ashkenazi Jewish). The patients were all seen by genetic counsellors or medical geneticists at one of the centre's affiliated hospitals: Chris Hani Baragwanath Hospital, Rahima Moosa Mother and Child Hospital, Helen Joseph Hospital, Charlotte Maxeke Johannesburg Academic Hospital and the Wits Donald Gordon Medical Centre. All data were obtained from either electronic or hard-copy patient records after ethics approval was obtained from the Human Research Committee (HREC) at the University of the Witwatersrand (ref. no. M230313, 18 May 2023). Records were anonymised and subsequently given unique record identity to maintain confidentiality.

Patient records were excluded where: (*i*) neither the patient nor their family history included a gynaecological cancer; (*ii*) family history was nonspecific (e.g. unconfirmed 'womb cancer'); or (*iii*) records were incomplete or unobtainable. Suitable records were reviewed to obtain relevant data (demographics, self-reported ancestry, relevant medical history, including cancer diagnosis and histology, genetic testing and family history) and organised using Research Electronic Data Capture (REDCap) software.

Categorical variables were summarised as frequencies and percentages, while normally distributed continuous variables were summarised using means and standard deviations (SDs). The association of positive test results with various patient factors such as self-reported ancestry was assessed using the χ^2 test for group comparison. Independent *t*-tests were used to determine significant differences between mean ages for different groups. This test was performed after data were determined to be normally distributed and have equal variance, using the Shapiro-Wilk test and Levene's mean test, respectively. The unequal variance *t*-test was performed as an alternative when data were not normally distributed, and the assumption of equal variance could not be made. Statistical significance was set at a $p<0.05$. Statistical analysis was done using the Real Statistics Resource Pack software (release 8.9.1) for Excel (Microsoft, USA).

Results

Patient characteristics

A total of 157 patients with either a personal or family history of gynaecological cancer were seen at the genetic counselling clinics between January 2003 and May 2023. However, only 104 records met inclusion criteria. The majority (45 (43.3%)) had a personal history of gynaecological cancer, of whom 37 (82.2%) had ovarian cancer and the remaining eight (17.8%) had uterine cancer. Ten patients (22.2%) had a family history of gynaecological cancer in addition to their diagnosis. Patient demographics are summarised in Table 2.

The majority of patients in the study, 73 (70.2%), were seen via private healthcare and the remaining 31 (29.8%) via public healthcare. There were differences in the distribution of self-reported ancestry among patients seen in private and public healthcare, highlighted in Fig. 1. Notably, indigenous African patients comprised the majority of those in public healthcare, but the minority of those in private.

For some analyses, reported ancestries were grouped: 'European' ancestry included self-reported European, Afrikaner and Ashkenazi Jewish ancestry; while 'non-European' ancestry included self-reported indigenous African and those who did not fall into the other recorded ancestral groups. The mean (SD) age of diagnosis for patients of non-European ancestry with a gynaecological cancer was 43.3 (4.3) years, 8.7 years earlier than those of European ancestry (51.9 years), which was statistically significant ($p<0.05$). Patients in public healthcare with gynaecological cancer took on average 7.4 years after their diagnosis to attend the genetics clinic, while those in private healthcare took on average 3.5 years. The delay between public and private was not statistically significant ($p>0.05$).

Table 3. Genetic testing performed for patients in our cohort (*N*=104)

Genetic testing	*n* (%)	Positive results, *n* (%)
Patients who underwent testing	96 (92.3)	36 (37.5)
Diagnostic testing	78 (81.3)	25 (32.1)
Family variant testing	18 (18.8)	11 (61.1)
Genetic tests conducted	100*	36 (36.0)
Type of genetic testing		
Public healthcare	33	9 (27.2)
Founder mutation†	4 (4.0)	1 (25.0)
BRCA1/2 sequencing	13 (13.0)	3 (23.1)
Local gene panel‡	9 (9.0)	1 (12.5)
Research§	2 (2.0)	2 (100)
International#	4 (4.0)	1 (25.0)
Family variant	1 (1.0)	1 (100)
Private healthcare	67	27 (40.3)
Founder mutation	7 (7.0)	1 (14.3)
BRCA1/2 sequencing	3 (3.0)	1 (33.3)
Local private¶	10 (10.0)	5 (50.0)
International**	30 (30.0)	10 (33.3)
Family variant	17 (17.0)	10 (58.8)

*Four patients each had one additional genetic test done after initial testing was negative.
†Testing for a limited number of specific mutations with a high prevalence in a population of distinct ancestry (e.g. *BRCA1* c.68_69delAG, *BRCA1* c.5266_5267insC, and *BRCA2* c.5946delT).
‡Genes included: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, PALB2, TP53.*
§More extensive/appropriate gene panel testing provided through research recruitment, which includes genes not available on the local gene panel.
#Gene panels for: breast and gynaecological cancers; breast cancer; colorectal cancer; common hereditary cancers; Lynch syndrome; paediatric solid tumour (on average, gene panels included 22 genes).
¶Four tests (40.0%) were *BRCA1/2* sequencing, 5 (50.0%) were nine-gene panels (*BRCA1, BRCA2, CDH1, PALB2, PTEN, RAD51C, RAD51D, STK11* and *TP53*) and 1 (10.0%) was a Lynch syndrome gene panel (*EPCAM, MLH1, MSH2, MSH6 and PMS2*).
**Breast cancer panel (13 genes); breast cancer STAT panel with *ATM* and *CHEK2* (9 genes); breast and gynaecological cancer panel (21 genes); breast and gynaecological cancer panel with preliminary-evidence genes (28 genes); colorectal cancer panel (21 genes); colorectal cancer guidelines-based panel (20 genes); common hereditary cancers panel (48 genes); Lynch syndrome panel (5 genes); paediatric solid tumours panel (54 genes).

Genetic testing

Across all 104 patients, 8 (7.7%) did not receive any genetic testing. The most common reason for this was that the patient was not an appropriate candidate for testing (i.e. unaffected and referred for their family history alone). Of the 96 (92.3%) who received genetic testing, the majority (67 (69.8%)) were patients from private healthcare (Table 3). A total of 100 tests were ordered, with four (4.2%) patients receiving additional testing after a negative result. Access to genetic testing in public and private healthcare was notably different (Table 3). Nearly all (17/18, 94.4%) family variant testing was done in private, and the majority (30/67, 44.8%) of private patients received testing by broader gene panels through international laboratories. In public healthcare, the most routine testing done was *BCRA1/2* sequencing (13/33, 39.4%), with only four (12.1%) having testing done internationally.

In all four instances (all in public healthcare) where additional testing was done, no PVs were detected. Private patients had a higher PV detection rate (27/67, 40.3%) than those in public healthcare (9/33, 27.2%). This difference was determined to be statistically significant ($p<0.05$). The odds that a patient who underwent genetic testing had a PV detected were higher in those who had private testing, compared with those who had public testing (odds ratio (OR) 1.5, 95% confidence interval (CI) 0.59 - 3.78).

Diagnostic yield

Of the 96 patients who underwent testing, 78 (81.3%) underwent diagnostic testing to try to establish a cause for their cancer. The remaining 18 (18.8%) had family variant testing to determine whether they had inherited a known (i.e. previously detected) PV. Diagnostic testing yielded 25 PVs across eight different genes (Fig. 2). No patient had multiple PVs detected, and so 25 (32.1%) patients received a positive genetic test result. Most PVs were found in *BRCA1* and *BRCA2*, with seven (28%) PVs detected in each. Fourteen (56%) patients were diagnosed with HBOC syndrome, and eight (32.0%) with Lynch syndrome.

In addition, diagnostic testing yielded 16 VUSs. One (1.3%) patient received both a PV and VUS, and two (2.6%) patients received multiple VUSs. In total, 12 (15.4%) patients received VUSs that could not clarify the cause of their cancer. Only 2/16 (12.5%) VUSs have been reclassified since testing was done: a *BRCA2* variant that was reclassified as B, and a *WT1* variant reclassified as LB. Of the remaining 14 VUSs, four (28.6%) were listed on ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) as 'conflicting interpretations of pathogenicity', having been reported differently by multiple submitters (i.e. laboratories).[25] Table 4 summarises all variants detected by diagnostic testing, their classification and the cancer history of the individual who was tested.

In terms of family variant testing, 18 relatives of patients were seen in our clinic, while an additional 22 (totalling 40) were tested through other laboratories. Of these, 24 (24/40, 60%) tested positive for the familial PV, and 17 (17/24, 70.8%) were asymptomatic at the time of testing.

Population differences in detection rate

Of the 104 patients included in the study, 78 (75%) had diagnostic testing, with 25 (32.1%) having a positive result (detecting a PV) and 53 (67.9%) not receiving a positive result (either negative or a VUS). These patients fell into one of five self-reported ancestral categories: Afrikaner (24, 30.8%), European (24, 30.8%), Ashkenazi Jewish (11, 14.1%) indigenous African (13, 16.7%) and 'other' (6, 7.7%). A statistically significant difference was found between a patient's self-reported population ancestry AND whether they were in public or private healthcare ($p<0.05$). Cramer's V value was calculated to be 1.14, which is considered a large effect size (df 1; $p>0.5$), therefore the observed statistical difference is unlikely due to chance. Furthermore, fewer PVs were detected in patients of non-European ancestry than those of European ancestry: 5 (20%) and 20 (80%), respectively. Similarly, only four (4/16, 25%) VUSs were detected in patients of non-European ancestry. The difference between genetic testing outcomes for these two broad, self-reported ancestral groups was determined to be statistically significant ($p<0.05$). The odds that a patient who underwent genetic testing had a PV detected were significantly lower in those of non-European ancestry (OR 0.7, 95% CI 0.22 - 2.21).

Discussion

Patient characteristics and demographics

As far as we are aware, this is the first study to assess genetic testing outcomes in patients with a personal or family history of gynaecological cancer in an SA population. Almost all the patients included were female, which was to be expected given the selection criteria. The cohort consisted of individuals from various ethnic backgrounds; however, indigenous African patients were the minority (15.4%), and so the cohort is not representative of the country's population distribution, where 81.0% are indigenous

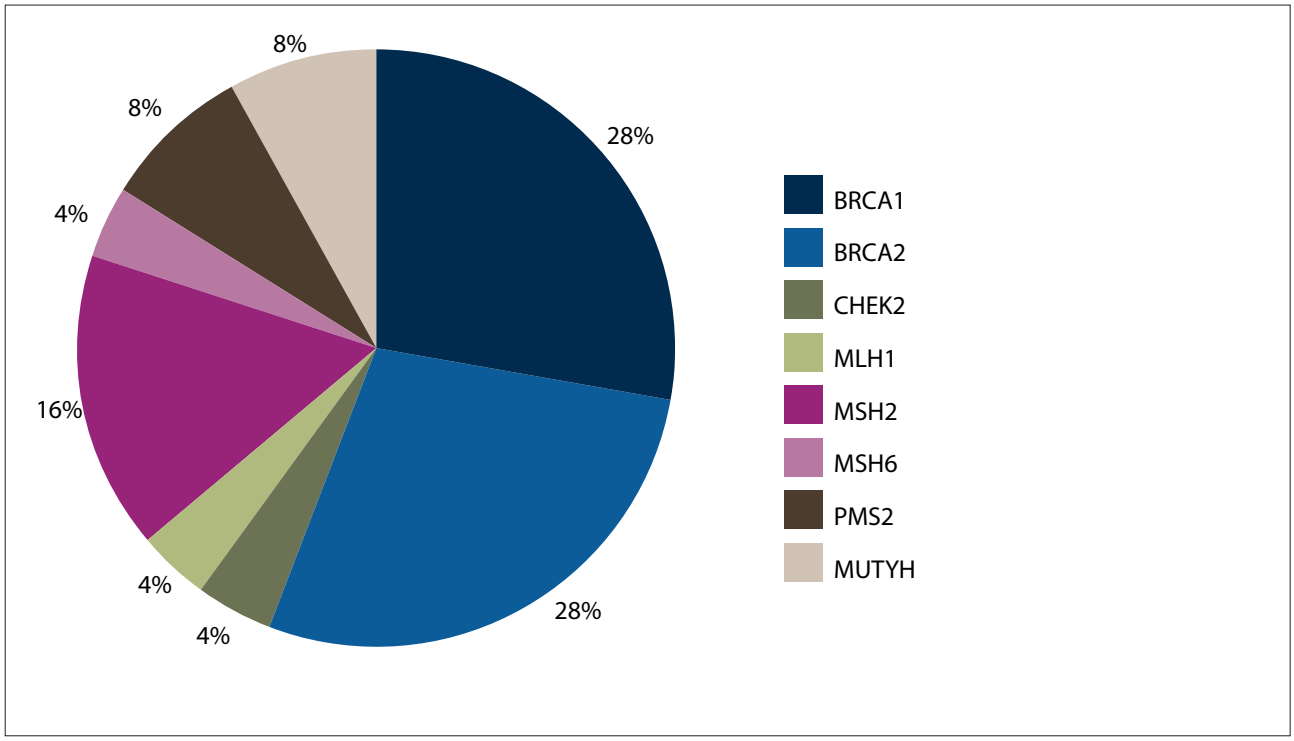

Fig. 2. Distribution of pathogenic variants (n=25) found across different genes.

African.[26] This underrepresentation reflects a concerning disparity that warrants critical attention, with clinical implications. While unexpected – given that the clinical genetics centre where this study was conducted holds the majority of its clinics in public healthcare, which services 84% of the population, 81% of whom are indigenous African[21,26] – this pattern aligns with global trends in access to genetic services.[27,28] Reasons for such pervasive disparity are multifactorial, with contributors related to the clinician, the patient and/or the healthcare system.

Clinicians may be unaware that genetic testing has clinical utility, or unsure of when to refer patients due to unfamiliarity with the specific risk factors pertinent to gynaecological cancers.[29,30] This knowledge gap seems to exist particularly for Lynch syndrome compared with HBOC syndrome.[31] Furthermore, clinicians who are familiar with the risk factors of heritable cancers may not know how to refer the patient to genetic services, or are simply unable to ensure that the patient attends the referral.[32] The health-seeking behaviours of patients accessing public healthcare is also known to reduce or delay presentation to tertiary hospitals. Reasons for this include lack of cancer knowledge and of the importance of screening, superstitions providing alternative explanations for disease and limited household income, which hinders transport to seek healthcare.[33-35] In public healthcare, the lack of genetic testing for Lynch syndrome is a significant limiting factor for diagnosing HCSs for patients, especially in the case of uterine cancers. In addition, the strain placed on public healthcare leads to resource scarcity, which negatively impacts patient care. This is further exacerbated by the lack of trained genetic counsellors.[36]

Taken together, these barriers highlight the need for further research to understand the complex and intersecting reasons for the under-representation of indigenous African patients in genetic testing services. Identifying the structural, cultural and clinical factors that perpetuate this disparity in an SA context is essential for developing equitable pathways to care. Future studies should prioritise inclusive recruitment strategies and community-engaged approaches that address these barriers and promote greater access to genetic counselling and testing across diverse SA populations.

Genetic testing

Although genetic testing in our cohort returned 25 PVs, two were in *MUTYH*, a gene associated with autosomal recessive polyposis.[6] Each *MUTYH* PV occurred in a heterozygous state, and therefore did not confer a diagnosis of an HCS. Thus, the diagnostic yield of genetic testing for our cohort was 29.5%, with the remaining 23 PVs detected conferring a diagnosis of an HCS. This is a higher yield than in previous studies investigating hereditary cancers, which have reported a yield of between 10% and 20%.[37,38] Despite over half (55/100, 55%) of the testing requested in our cohort being done by multi-gene panel testing, only 16 VUSs were detected. The prevalence of VUS detection is known to increase when multiple genes are analysed simultaneously, or when patients belong to underrepresented population groups, such as indigenous African.[39] The combination of high PV and low VUS detection could indicate that for our cohort, the referral to genetics was generally appropriate. However, another contributor may be the population bias towards European ancestry. Roughly 90% of VUSs are reclassified as benign, and attributed to normal variation, although the few that are later determined to be pathogenic have clinical utility.[40] In our cohort, only two VUSs (12.5%) have been reclassified as benign/likely benign. Ten (62.5%) have remained unchanged for, on average, 3 years, and four (25%) variants are currently reported to have conflicting interpretations of pathogenicity. In line with international guidelines,[12] patients in this cohort were counselled at the time of testing that VUSs do not influence clinical management, but may be reclassified over time. Patients were advised to remain in contact with the genetics clinic, and where feasible, efforts are made to re-curate a variant every 3 - 5 years. However, resource limitations in the public healthcare sector present challenges for systematic re-contact, and patients are therefore also encouraged to initiate follow-up where possible. With gene panels becoming the standard of care, routine

Table 4. Genetic variants and classification summary

Gene	Variant	Classification	Self-reported ancestry	Proband cancer	Family history of gynaecological cancer (relative)
ATM	c.946T>A (p.Tyr316Asn)	VUS	European	CRC	OC (SDR)
BRCA1	c.1A>G (p.Met1Val)	P	European	OC	OC (FDR)
	c.2008G>T (p.Glu670Ter)	P	Indigenous African	OC	n/a
	c.2641G>T (p.Glu881Ter)	P	Afrikaner	OC	OC (FDR)
	c.3263T>A (p.Val1088Asp)	VUS	European	OC	n/a
	c.45dup (p.Asn16Ter)	P	Afrikaner	BC	OC (FDR)
	c.5266dup (p.Gln1756fs)	P	Ashkenazi Jewish	BC	OC (FDR)
	c.5533dup (p.Tyr1845fs)	P	Afrikaner	BC and UC	n/a
	c.68_69del (p.Glu23fs)	P	Ashkenazi Jewish	n/a	OC (1 FDR, 1 TDR)
BRCA2	c.3599_3600del (p.Asp1199_Cys1200insTer)	P	Afrikaner	BC	OC (2 FDR), UC (2 FDR, 1 TDR)
	c.5763del (p.Phe1921fs)	P	European	OC	n/a
	c.5946del (p.Ser1982fs)	P	Ashkenazi Jewish	BC	OC (SDR)
	c.6761_6762del (p.Phe2254fs)	P	European	OC	OC (FDR)
	c.7934del (p.Arg2645fs)	P	Afrikaner	OC	OC (FDR)
	c.8954-2A>G	P/LP	Indigenous African	UC	n/a
	c.9976A>T (p.Lys3326Ter)	VUS →B	European	OC	n/a
CHEK2	c.1263del (p.Ser422fs)	P	European	BC	UC (FDR)
	c.538C>T (p.Arg180Cys)	Conflicting interpretations of pathogenicity	Afrikaner	n/a	UC (2 FDRs)
FANCM	c.3998A>C (p.Gln1333Pro)	VUS	Afrikaner	Melanoma	OC (FDR)
GPC3	c.49A>T (p.Ser17Cys)	VUS	Afrikaner	BC and OC	n/a
HOXB13	c.153G>T (p.Leu51Phe)	VUS	Indigenous African	OC	UC (SDR)
MLH1	c.2108_2117del (p.Glu703fs)	P	Other	CRC	UC (SDR)
MSH2	c.1046C>G (p.Pro349Arg)	P	Indigenous African	UC	
	c.1340_1341insGG (p.Phe447fs)	P	European	OC	n/a
	c.2502_2508del (p.Asn835fs)	P	European	CRC	OC (two FDRs)
	Deletion (Exons 12-16)	P	Other	UC	n/a
MSH3	c.2659G>A (p.Asp887Asn)	VUS	Afrikaner	OC	n/a
MSH6	c.1871del (p.Gly624fs)	P	European	UC	UC (FDR)
MUTYH	c.1103G>A (p.Gly368Asp)	P	Afrikaner	n/a	OC (FDR)
	c.1187G>A (p.Gly396Asp)	P	European	OC	n/a
	c.14_16dup (p.Arg5_Ala6insGly)	VUS	Ashkenazi Jewish	OC	n/a
NBN	c.628G>T (p.Val219Phe)	Conflicting interpretations of pathogenicity	Afrikaner	OC	n/a
PMS2	c.137G>A (p.Ser46Asn)	P	European	n/a	UC (FDR)
	c.2012C>T (p.Thr671Met)	Conflicting interpretations of pathogenicity	European	OC	n/a
	c.2478G>C (p.Glu826Asp)	VUS	Indigenous African	OC	UC (SDR)
	c.736_741delCCCCCTins11 (p.?)	P	European	n/a	OC (FDR)
POLE	c.3230G>A (p.Arg1077His)	Conflicting interpretations of pathogenicity	Afrikaner	BC & OC	n/a
TSC2	c.3578G>T (p.Gly1193Val)	VUS	Indigenous African	OC	UC (SDR)
WT1	c.203A>T (p.Gln68Leu)	VUS →LB	Indigenous African	OC	n/a
XRCC2	c.514A>G (p.Thr172Ala)	VUS	Afrikaner	n/a	OC (FDR)

Proband = patient seen for genetic counselling; VUS = variant of unknown significance; CRC = colorectal cancer; OC = ovarian cancer; SDR = second-degree relative; P = pathogenic; FDR = first-degree relative; TDR = third-degree relative; BC = breast cancer; UC = uterine cancer; LP = likely pathogenic; B = benign.

Variant reclassification indicated by arrow.

re-analysis of VUSs and variants with conflicting interpretations remains critical, particularly in underrepresented populations where genomic reference data are limited.[41]

Nearly all PVs detected were associated with either HBOC syndrome or Lynch syndrome, which was expected given that these are two of the most common HCSs.[42] The high proportion of *BRCA1/2* pathogenic variants may also be due to our cohort having a higher incidence of ovarian than uterine cancer, with PVs in *BRCA1* and *BRCA2* being associated with a significant ovarian cancer risk (44% and 17%, respectively).[43] Similarly, a high *MSH2* PV detection can be explained by the fact that it confers not only the highest overall cancer risk, but the highest risk for uterine and ovarian cancers (46% and 17%, respectively).[44]

Non-European ancestry individuals had a 30% lower likelihood of having a pathogenic variant identified, potentially owing to factors such as limited access to testing, and population-specific considerations. Patients in public healthcare, who are more often of non-European ancestry, face constraints in comprehensive genetic testing, which is limited to an eight-gene panel focused on breast and ovarian cancer genes,[20] placing a significant limitation on PV detection in the context of gynaecological cancers. Furthermore, genetic research has identified several founder mutations for those of Afrikaner and Ashkenazi Jewish ancestry, improving the likelihood of genetic testing in these populations to yield a PV.[22,45] It is also possible that the cancers seen in indigenous African populations are caused by genes yet to be identified, hence not included in current testing.[46] In addition, population factors related to disease penetrance may also be reducing PV detection rates in non-Europeans. Numerous studies looking at heritable cancers have shown that indigenous African patients diagnosed with cancer are unlikely (<10%) to have a family history of cancer.[47-49] This demonstration of reduced disease penetrance may in turn limit the referrals and thus testing of cancer patients of African ancestry.

After reviewing the testing performed, 36 (37.5%) tests were deemed insufficient owing to technical limitations raising concerns for false negatives. Instances of insufficient testing occurred when, based on personal and familial cancer history, the testing conducted did not offer sufficient coverage (e.g. founder mutations testing only), or genes were excluded from analysis that could be responsible for the cancer history (e.g. *BRCA1/2* sequencing only). Of these, 17 (47.2%) were patients in public healthcare and 19 (52.8%) were private patients. In public healthcare, families presenting with a history of uterine and colon cancer suggestive of Lynch syndrome do not receive sufficient testing owing to the lack of a panel of genes associated with colorectal cancers. Given the declining costs of next-generation sequencing and the growing evidence supporting the utility of multigene panels in detecting a broader spectrum of hereditary cancer syndromes,[50] we recommend that future efforts include a cost-benefit analysis of implementing panel-based testing in the SA public healthcare system. Investment in such testing could yield long-term savings through early detection and prevention, while improving patient outcomes.[51] Furthermore, we advocate for policy change that integrates comprehensive genetic testing into public healthcare pathways, supported by national guidelines and pilot implementation programmes. Such changes are critical to reducing the genetic diagnostic gap and enabling equitable access to precision oncology.

Across the 20-year period, it was noted that the number of patients seen by our genetic services increased substantially. From the year 2000 in intervals of 5 years (e.g. 2000 - 2004, and then 2005 - 2009, etc.), the number of patients seen were 1, 4, 11, 23 and 46, respectively. This increase in patients could be attributed to the expansion of genetic services since their inception in the late 1990s.[52] Equally important is the increase in visibility of genetic services among healthcare providers through the establishment of clinical genetic centres.[29] Expansion has also followed the trend of improved genetic testing in the public healthcare sector.

Family variant testing

Nearly all family variant testing was done in the private sector, with only one patient in our cohort having family variant testing in the public healthcare system. Internationally, the uptake of family variant testing for HCSs by at-risk relatives is considered to be low. Investigations have shown that possible reasons include family communication, family history and experience related to cancer, fear of a positive result and accessibility of testing.[53-55] Of relevance to our cohort is that such testing in the private sector was most often done through an international laboratory that offered free family variant testing in the event that a PV was found, which is known to significantly improve uptake.[53] Although factors such as family communication cannot be excluded as a cause for the uptake discrepancy between the public and private sectors, these are beyond the scope of this study.

From the diagnostic yield in our cohort, 40 additional individuals presented for family variant testing. The majority of individuals who tested positive for a familial variant (24/40, 60%) were asymptomatic at the time of testing. Family variant testing is less costly than diagnostic testing, and inherently less resource-intensive (in laboratory, interpretation and counselling time).[18] Furthermore, identifying asymptomatic relatives who have inherited the familial variant helps to avoid the high-cost care of cancer treatment by enabling disease prevention measures. For asymptomatic women diagnosed with HBOC syndrome, increased mammography screening has been shown to reduce overall breast cancer mortality by up to 19%.[56] In addition, a prophylactic mastectomy could reduce breast cancer mortality by between 81% and 100%, while prophylactic bilateral salpingo-oophorectomy (BSO) is associated with a decreased incidence of both breast and ovarian cancer, together with a reduction of all-cause mortality by between 55 and 100%.[15,57] These surgeries can be considered in asymptomatic women diagnosed with Lynch syndrome, but should be tailored based on the patient's causative gene, family cancer history, comorbidities, whether childbearing is complete and, in the case of BSO, menopause status.[15] Owing to their prevalence and treatability, population-based screening to identify asymptomatic carriers by genetic testing has been proposed for Lynch syndrome and HBOC syndrome.[38] The challenges that would need to be overcome in the resource-limited context of SA, which include costs, obtaining informed consent and variant interpretation, make this far from feasible. Predictive testing of at-risk family members, however, stands as an attractive, cost-effective alternative that should be considered.[18]

Limitations

This was a retrospective study performed at a single institution with inherent selection bias, including the error that may be associated with relying on patient recall in a genetic counselling consultation. Patient records that were incomplete or unobtainable limited the number of patients that could be included. The relatively small patient cohort and the large data collection period may have reduced the power to detect some of the associations between patient factors and genetic testing outcomes. In particular, genetic testing availability was not consistent across the collection period. The small patient cohort also limited the extent to which the effect that patient characteristics had on testing could be investigated. Furthermore, our

sample included predominantly white patients of either European or Afrikaner ancestry, and so is unlikely to be representative of the genetic testing outcomes for indigenous African patients with a personal or family history of gynaecological cancer.

Conclusion

With the advancement of genetic testing in the era of sequencing, and improved understanding of cancer heritability, an increasing number of cancer patients are referred to genetic services. Genetic testing can identify those with an inherited cancer syndrome, which can improve the care and management available for both the patient and their family. This study highlights disparities that exist not only in genetic testing availability, but also in clinic attendance, between the public and private healthcare sectors, which likely limit the ability to diagnose hereditary cancer syndromes associated with gynaecological cancers in public hospitals.

Data availability. Data available from authors upon request.

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