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Review

The implementation and outcome of a breast cancer genetic counselling service at Potchefstroom Hospital: a model for outreach

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Aim

Breast cancer is the most prevalent cancer in South African females, making up 27.1% of all histologically diagnosed cancers in 2020. Although genetic technology and awareness of genetic counselling have improved, genetic counselling services in South Africa remain largely inaccessible. Clinical genetic services are only formally available in four South African provinces and few outreach programmes exist for small towns and cities. Until 2019, genetic counselling services were unavailable in the North West province; however, since then, genetic counsellors from the National Health Laboratory Service and the University of the Witwatersrand have provided genetic counselling services to patients at the Breast Clinic at Potchefstroom Hospital regularly each year.

Method

The aim of this pilot study was to perform a retrospective file review and report on the implementation and outcomes of the genetic counselling service at the Breast Clinic at Potchefstroom Hospital, from its inception in 2019, until November 2022. Fifty-two patients attended a genetic counselling consultation during that period.

Results

The majority of patients (83.7%) were diagnosed with an invasive ductal carcinoma, and 57.7% of the patients had a family history of cancer. A total of 62.8% of patients had a histologic grade 3 tumour. A total of 25.5% (12/47) of patients tested positive for a pathogenic variant in *BRCA1* or *BRCA2*. A total of 45 at-risk first-degree relatives were identified who could benefit from predictive testing.

Conclusions

This study highlights the benefit of offering clinical genetics services through outreach clinics. Being able to offer this service is not only beneficial for the management of the affected individuals, but also for their at-risk relatives. The initiative serves as a positive example of how limited resources can be extended to benefit patients.

Introduction

Breast cancer is the most prevalent cancer among females in South Africa, contributing 27.1% towards all histologically diagnosed cancers in females in 2020.[1] In the past two decades, genetic research and testing for patients with cancer have improved disease management and patient outcomes, with genetic testing becoming an integral part of clinical practice in many centres worldwide.[2] Identifying pathogenic variants in cancer-predis-

posing genes has implications for patients and their family members, with risks of having inherited the pathogenic variant as high as 50% in at-risk relatives.[3] Awareness of a genetic predisposition to breast cancer opens the door to increased screening, early diagnosis, and new treatment and preventative options.[2]

The most common inherited breast cancer syndrome is Hereditary Breast and Ovarian Cancer (HBOC) syndrome, which is caused by pathogenic variants in the *BRCA1* and *BRCA2* genes. This condition is inherited in an autosomal dominant manner. It confers a lifetime breast cancer risk of up to 72% in females and up to 8% in males, and an ovarian cancer risk of up to 44%. In addition, individuals who carry a pathogenic variant in one of the *BRCA* genes are also at increased risk for developing other cancers, such as prostate and pancreatic cancer.[4] Genetic counselling is essential in the multi-disciplinary management of individuals at risk of an inherited cancer syndrome. Genetic counsellors are trained to identify high-risk individuals and families, facilitate appropriate genetic testing for patients and their family members, and explain the clinical and familial implications of genetic test results.[5] Patients should ideally receive genetic counselling before and after undergoing genetic testing.[6]

Genetic testing for HBOC in the state healthcare system in South Africa is available through the National Health Laboratory Service (NHLS) in Bloemfontein in the Free State. Prior to May 2021, the laboratory offered next-generation sequencing (NGS) and deletion/duplication analysis of only the *BRCA1* and *BRCA2* genes for patients with a personal and/or family history of breast cancer or associated cancers. After May 2021, the laboratory offered NGS of eight genes associated with inherited breast cancer (*BRCA1*, *BRCA2*, *TP53*, *PALB2*, *ATM*, *CHEK2*, *BARD1* and *BRIP1*), as well as deletion/duplication analysis of the *BRCA1* and *BRCA2* genes.

There is a lack of literature on establishing genetic services in low- to middle-income countries. In South Africa, the resource-constrained healthcare system and the high burden of non-communicable diseases[7] have prevented genetic services from being made widely available. Although genetic technology has improved, and there is an increased awareness of genetic counselling globally,[8] genetic counselling services in South Africa remain largely inaccessible to most of the population. Currently, clinical genetic services offered by registered genetic counsellors and medical geneticists are only available in two of the nine provinces in South Africa: Gauteng and the Western Cape. Genetic services are also available to patients in KwaZulu-Natal and the Free State.[9] Clinical genetic services in South Africa are historically based in academic and private hospitals, and few outreach programmes exist from those centres to small towns and cities.[9] Until 2019, genetic counselling services were not available in public hospitals in the North West province of South Africa, and any discussions about genetics with patients were poorly provided by physicians with heavy clinical workloads and little genetics training.[10] Furthermore, many breast cancer patients in South Africa receive a late diagnosis, often presenting with advanced stages of the disease. Factors such as inadequate education and a lack of awareness of breast cancer among patients, as well as inadequacies in the healthcare system, have been associated with advanced-stage diagnosis in South African women.[11] By introducing a genetic counselling service within a breast clinic, education about breast cancer and the importance of early screening could mitigate some of these issues.

There is an increasing need to expand the availability of clinical genetic services beyond the country's main metropolitan areas. The South African guidelines on breast cancer management recommend genetic counselling and testing as part of the comprehensive management of patients with breast cancer.[12] In March 2019, a collaboration was established between the Division of Human Genetics, NHLS and the University of the Witwatersrand (Wits), and the Breast Clinic within the Department of Surgery at Potchefstroom Hospital in the North West province. Potchefstroom Hospital is a regional hospital which serves the entire population of JB Marks municipality and some self-referred patients from surrounding provinces and towns, like Carletonville and Fochville in Gauteng, and Parys and Viljoenskroon in the Free State. The Department of Surgery offers services to about 70 patients per day in the outpatient department and about 40 inpatients per day. The Breast Clinic within the Department of Surgery has been running since 2012.[13] An agreement was established whereby genetic counsellors from the NHLS/Wits, based in Gauteng, would travel through to Potchefstroom to provide genetic counselling services to patients at the Breast Clinic at Potchefstroom Hospital at regular intervals during the year. The patients were identified by local surgeons as fulfilling the criteria to be referred for genetic counselling and were pre-booked to attend these clinics.

The aim of this pilot study is to report on the implementation and outcome of the genetic counselling service at the Breast Clinic at Potchefstroom Hospital.

Methods

This study was a retrospective file review of all patients referred for genetic counselling at the Breast Clinic, Potchefstroom Hospital, from the inception of the genetic counselling service in 2019 until November 2022. Ethics clearance was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (certificate number: M180506).

Patients

This study involved patients managed through an outreach genetic counselling service to Potchefstroom Hospital held over four years. During 2019, three genetic counselling clinics were held. Due to the COVID-19 pandemic, only one clinic was held in 2020. Four genetic counselling clinics were held in both 2021 and 2022. Pa-

tients who fulfilled one or more of the following inclusion criteria were referred for genetic counselling:

- Breast cancer diagnosed ≤ 50 years of age
- Bilateral breast cancer
- Triple-negative breast cancer, regardless of age
- First-degree relatives of positive pathogenic variant carriers
- Strong family history of breast cancer, irrespective of age
- Primary breast cancer diagnosed more than once in the same breast
- A male patient diagnosed with breast cancer

Data collection

The genetic counselling patient files that contained histology reports, family pedigrees, clinical notes, and genetic test results were assessed for this pilot study. Data were extracted from the individual files and collated in an Excel spreadsheet.

Risk assessment

The genetic counsellors at the NHLS/Wits always perform a 'manual risk assessment' on patients who come for counselling regarding a personal and/or family history of breast cancer. This assessment takes into consideration the family pedigree, how many relatives are affected with cancer, what types of cancers are present in the family, as well as the age of onset of cancer diagnoses. Patients are classified as being at low, average, moderate or high risk of having an inherited cancer syndrome. Low risk suggests the risk of developing cancer is the same as the population risk; average risk is slightly higher than the general population risk. Moderate risk is an intermediate risk, which is higher than average risk and individuals in this group require increased screening. High risk is commonly associated with a genetic risk, where the risk for cancer development is increased and intensive surveillance is required. Some of the following characteristics are usually present in moderate- to high risk families with cancer: at least three first-degree relatives affected with associated cancers (e.g., breast and ovarian); when the cancers develop at a younger age of onset than the average for particular cancer(s) (under 50 years for breast cancer, under 60 years for ovarian cancer); when unusual or uncommon cancers occur; when an individual has multiple primary tumours; and when individuals belong to higher risk founder population groups. It is important to note that little is known about the prevalence of inherited breast cancer syndromes among the black South African population. In addition, data have shown that a diagnosis of breast cancer under 50 years of age alone in a black South African female raises concern for an inherited breast cancer syndrome.[14] Such a patient would be classified as moderate risk. In this study, individuals classified as moderate or high risk based on the manual risk assessment performed by the genetic counsellor were offered genetic testing.

Statistical analysis

The Excel Statistical Analysis Application was used for descriptive statistical analysis. Normally distributed continuous variables were presented as means ± standard deviations (SD). Categorical data were presented as frequencies and percentages.

Results

Study population

From July 2019 to November 2022, there were 154 patients diagnosed with breast cancer at Potchefstroom Hospital. Among those diagnosed with breast cancer, 55/154 (35.7%) patients were eligible for referral for genetic counselling based on the pre-defined inclusion criteria. A total of 49/55 (89.1%) of the patients diagnosed with breast cancer attended a pre-test genetic counselling consultation. Additionally, three asymptomatic individuals with a family history of cancer also attended a pre-test genetic counselling consultation at Potchefstroom Hospital. A total of 22 (42.3%) patients attended genetic counselling in 2019, four (7.7%) patients attended in 2020, 15 (28.8%) attended in 2021 and 11 (21.2%) attended in 2022.

The characteristics of the 52 patients who attended a pre-test genetic counselling consultation are provided in Table 1. The mean age of the patients was 44.7 ± 8.5 years and 96.2% (50/52) of the patients were female. A total of 94.2% (49/52) of the patients had been diagnosed with breast cancer, with a mean age of diagnosis of 41.4 ± 8.6 years. The remaining three asymptomatic patients were referred for genetic counselling due to their family histories of breast cancer. A total of 19.2% (10/52) of the patients had a strong family history of cancer, while 42.3% (22/52) of the patients had no family history of cancer.

Breast cancer histology

As described in Table 1, a total of 49 of the 52 patients were diagnosed with breast cancer, and histology results were available for these patients. The majority of these patients (95.9%; 47/49) were diagnosed with invasive ductal carcinoma. A total of 59.2% (29/49) of patients had a grade 3 tumour, and 28.6% (14/49) had triple-negative receptor status (oestrogen-, progesterone- and Her2-receptor negative) (see Table 2).

Genetic test results

A total of 45/49 (89.8%) patients diagnosed with breast cancer underwent diagnostic genetic testing. Patients seen before May 2021 (28/45; 62.2%) received testing for variants in the *BRCA1* and *BRCA2* genes only. Patients seen after May 2021 (16/45; 35.6%) received testing for eight genes associated with inherited breast cancer syndromes. One individual diagnosed with breast cancer un-

Table 1. Characteristics of the patients* referred for Genetic Counselling at the Breast Clinic, Potchefstroom Hospital

Characteristics	Number of patients (%) (n=52)
Breast cancer diagnosed ≤ 50 years of age	46 (88.5)
Bilateral breast cancer	0 (0.0)
Triple-negative breast cancer, regardless of age	14 (26.9)
First-degree relatives of positive pathogenic variant carriers	2 (3.9)
Strong family history of breast cancer, irrespective of age	10 (19.2)*
Primary breast cancer diagnosed more than once in the same breast	0 (0.0)
A male patient diagnosed with breast cancer	1 (1.9)

*Those that were classified as moderate to high risk following a manual risk assessment

Table 2. Breast cancer histology

Breast Cancer Histology	Number (%)
	(n=49)
Type of Tumour	
Invasive ductal carcinoma	47 (95.9)
Ductal carcinoma *in situ*	2 (4.1)
Grade of Tumour	
1	3 (6.1)
2	17 (34.7)
3	29 (59.2)
Tumour Molecular Subtype	
Luminal A	20 (40.8)
Luminal B	10 (20.4)
Her2-enriched	5 (10.2)
Triple negative	14 (28.6)

derwent diagnostic genetic testing for a known familial pathogenic variant in *BRCA2*. Of those who did not have a personal history of breast cancer, one individual underwent predictive testing for a familial pathogenic variant in *BRCA2*, and one individual underwent diagnostic genetic testing due to a significant family history of cancer. Therefore, a total of 47 patients chose to proceed with genetic testing due to their personal and/or family history of breast cancer. Of the four individuals with a personal history of breast cancer who did not undergo genetic testing, one was classified as low risk and another as average risk and, therefore, were not offered testing. The remaining two individuals declined testing.

A total of 25.5% (12/47) of the patients tested had a pathogenic variant in *BRCA1* or *BRCA2*. One or more variants of uncertain significance were detected in 21.3% (10/47) of the patients, and 53.2% (25/47) of the patients received a negative result. Among the 12 patients who received a positive result, 33.3% (4/12) underwent a risk-reducing contralateral mastectomy at Potchefstroom Hospital. Of the 12 positive individuals, 45 at-risk relatives were immediately eligible for cascade testing.

A total of 11 variants of uncertain significance were detected in 10 patients. One patient had two variants of uncertain significance, one in *BRCA1* and one in *BRCA2*. The remaining nine patients had one variant of uncertain significance. These were detected in one of four genes: *BRCA1* (2/9), *BRCA2* (3/9), *PALB2* (2/9) and *ATM* (2/9). None of these variants have been reclassified and are, therefore, not clinically actionable (Table 3).

Discussion

Breast cancer histology

Whilst acknowledging the small sample size, an interesting finding was the absence of invasive lobular breast cancer. Invasive lobular breast cancer accounts for approximately 10% of all invasive breast carcinomas.[15] Another interesting finding was that the majority (59.2%) of women with breast cancer had grade 3 tumours. The rate of grade 3 tumours has been reported to be significantly higher in individuals with pathogenic variants in *BRCA1* compared to those with pathogenic variants in *BRCA2* or those without a positive genetic test result.[16] Of the five patients with a pathogenic variant identified in *BRCA1*, all presented with a grade 3 tumour. Of the seven patients with a pathogenic variant identified in *BRCA2*, one was asymptomatic at the time of testing, and the remainder presented with a grade 2 (3/6) or grade 3 (3/6) tumour.

Triple-negative breast cancer is thought to account for approximately 15-20% of all breast cancers on a global level.[17] This study revealed that 38.8% of the patients presented with triple-negative breast cancer, which is higher than the global prevalence. Morris et al. describe triple-negative breast cancer as being more common in African-American patients than in Caucasian patients (20.8% vs 10.4%; $P < 0.0001$).[18] Given the fact that triple-negative breast cancer is generally aggressive and challenging to treat due to its invasive nature and poor re-

Table 3. Outcome of genetic testing in 47 patients

Genetic testing results	n (%)
Positive	12 (25.5)
BRCA1	5 (41.7)
BRCA2	7 (58.3)
Negative	25 (53.2)
Variant of uncertain significance (one or more)	10 (21.3)

sponse to treatment,[17] early breast screening among women of black South African ancestry is warranted.[18] Another explanation for the increased prevalence of triple-negative breast cancer in this study may be due to selection bias, as having triple-negative breast cancer is a criterion for genetic testing. A study by Kakudji et al. conducted in the same setting found that 22.4% of patients presented with triple-negative breast cancer, which is similar to the global prevalence.[19]

Management and surveillance

Pedigree analysis of the individuals who tested positive for a pathogenic variant revealed 45 at-risk adult family members. Knowing one's genetic status can determine one's medical management. Management and surveillance strategies can be established for carriers of a pathogenic or likely pathogenic *BRCA1/2* variant. Similarly, for those who test negative, the need for additional investigations can be mitigated.[18] Furthermore, one's genetic status can influence future reproductive options, particularly in cases where carriers want to prevent passing a pathogenic variant on to their children.[19]

The risk-management recommendations for carriers of a pathogenic or likely pathogenic *BRCA1/2* variant are based on the early age of disease onset and the significantly increased risks for malignancy. These management options include increased surveillance involving annual breast MRI with contrast, risk-reducing surgery such as bilateral total mastectomy and bilateral salpingo-oophorectomy, and chemoprevention. All recommendations are based on an individual's sex assigned at birth.[20] With the appropriate management and surveillance, pathogenic variant carriers have the opportunity to detect cancer at early stages when there is an increased likelihood for successful treatment outcomes or to reduce their risk by undergoing risk-reducing surgeries.[21] As seen in the current study, 33.3% (4/12) of patients who received a positive genetic testing result underwent a risk-reducing contralateral mastectomy. This procedure would not have been made available to them without a positive genetic test result. An individual from a family with a known pathogenic or likely pathogenic variant in *BRCA1/2* who tests negative for the familial variant should be managed according to the cancer screening recommendations for the general population. In these circumstances, a negative result provides significant reassurance about their lifetime risks for developing cancer.[20]

At-risk relatives

The study revealed 45 at-risk relatives who could benefit from genetic counselling and testing. Whether or not they take up the offer remains to be determined over time. At the time of the study, only two at-risk family members chose to pursue genetic counselling and predictive testing through the clinic at Potchefstroom Hospital. Cascade testing of at-risk family members is often a contentious issue and a widely researched topic in the field of clinical genetics. The disclosure of familial cancer risks is influenced by a multitude of factors, including the quality of intrafamilial relationships, psychological distress, experience of cancer within a family, and cultural-based aspects.[22] A South African study by Benn et al. highlighted the significance of cultural barriers to breast cancer care and that culturally relevant navigation improves patient adherence and overall patient care.[23]

In addition to a reluctance to share genetic testing results, Menko et al. highlight that family members living overseas and having limited pedigree information can hinder cascade testing.[24] Pedigrees are drawn up based on the information given to the genetic counsellor by the patient, so limited or incorrect family history information might be conveyed. Disclosure of genetic test results among family members was not reported as an issue in the study by Finlay et al.[25] Still, low uptake of genetic testing was reported among at-risk individuals, particularly among men, second-degree relatives, and those from the paternal side of the family.[25] Blomen et al. showed similar results with male at-risk relatives in particular, showing higher levels of anxiety and uncertainty about the benefits of genetic testing.[22] A study focusing on women with pathogenic variants in *BRCA1/2* reported that disclosure of results to family members was not realised. It emphasised that the oncology team needed to play a more significant role in preparing *BRCA*-positive women to share their genetic test results.[26] This is another reason genetic counsellors are crucial to managing such patients and an area of focus for the clinic going forward.

A South African study investigating the uptake of cascade testing among family members of patients with cystic fibrosis revealed that testing uptake was highest when genetic counselling was integrated into hospital-based management clinics.[27] This supports the need for genetic counsellors to be physically present and available within breast clinics. Furthermore, increasing patient education on breast cancer through access to genetic counsellors and improving access to culturally similar genetic counsellors could help decrease some of the known barriers to cascade testing.[23]

Limitations and challenges

This review of the genetic counselling service at Potchefstroom Hospital identified three limitations. First, patients seen before May 2021 were only offered *BRCA1* and *BRCA2* testing. Despite *BRCA1* and *BRCA2* being most commonly associated with inherited breast cancer, there are other associated genes. Individuals seen for genetic counselling before May 2021 who tested negative for a pathogenic, or likely pathogenic variant, in *BRCA1* and *BRCA2* should be offered more extensive genetic testing. Second, the testing currently offered through the state healthcare system in South Africa does not include all moderate-risk genes associated with the development of breast cancer, such as *CDH1*, *STK11* and *PTEN*. The third limitation is that only two at-risk family members chose to pursue genetic counselling and predictive testing through the clinic at Potchefstroom Hospital. However, this may not be a true representation of the uptake of cascade testing among the at-risk relatives identified in this study, as any cascade testing performed at another genetic centre, or beyond this study's timeframe, would not have been recorded. Therefore, the impact of the genetic counselling and testing service could not be assessed beyond the personal and clinical utility for the patients diagnosed with breast cancer. A larger, national study is underway to assess the uptake of genetic counselling and testing among at-risk relatives in a larger cohort over a fixed time period.

The main challenges identified through this research were logistical and financial. From a logistical perspective, travelling into Potchefstroom from Johannesburg and back is time-consuming and removes genetic counselling staff from Johannesburg-based clinics. Financially, the cost of travel and the cost of the increase in genetic testing borne by the Department of Surgery were other identified challenges.

Recommendations

This study presents the outcomes of the very first genetic counselling clinic for breast cancer at Potchefstroom Hospital. The collaboration of the Department of Surgery at Potchefstroom Hospital and the Division of Human Genetics at the NHLS and Wits has been successful. The implementation of quarterly genetic counselling outreach clinics has resulted in several patients and, in turn, their relatives being made aware of their genetic status. Knowledge of their genetic status has empowered patients to make appropriate decisions about their health as well as allowing their doctors to tailor their management and provide opportunities for early intervention. This study exemplifies how patients in other South African centres could benefit from genetic counselling and testing through a multi-disciplinary approach. The study also provides anecdotal evidence to suggest that this outreach model may also be suitable for patients with other genetic conditions. However, the authors acknowledge that other models may be required for implementation in different settings, especially in cases where there are significant logistical and financial limitations. Further research is required to fully explore various models of implementation and their implications for patients and at-risk relatives.

Conclusion

In conclusion, this study reports the outcomes of successfully integrating genetic counselling services into a breast clinic in a province in South Africa where clinical genetic services are typically unavailable. Most patients who were referred for genetic counselling presented with high-grade invasive ductal carcinoma. Over four years, 49 patients underwent genetic testing. Pathogenic variants in the *BRCA1* or *BRCA2* genes were identified in 25.5% of the study population and 45 at-risk individuals were identified. Many individuals benefited from this outreach service, particularly the 49 patients whose clinical management is now better informed based on their genetic test results. This study further highlights that patients receive optimal care when disciplines work together.

The successful implementation of this service highlights the importance of inter-departmental collaboration. It serves as a positive example of how limited resources can be extended for the benefit of the patient population. Consistent service provision, at regular intervals throughout the year, has allowed for an increasing number of appropriate patient referrals to genetic counselling and for continuity of care. Local healthcare providers are able to identify and refer appropriate patients, and genetic counsellors can offer pre-test genetic counselling consultations and result-delivery consultations as well as assisting with management going forward.

Abbreviations

Abbreviation	Description
HBOC	hereditary breast and ovarian cancer syndrome
NGS	next generation sequencing
NHLS	National Health Laboratory Service
SD	standard deviation
Wits	University of the Witwatersrand

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