ASSESSMENT OF GENETIC COUNSELLING AND TESTING OF PATIENTS DIAGNOSED WITH INVASIVE BREAST CARCINOMA IN TWO SOUTH AFRICAN BREAST UNITS

by

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LIST OF ABBREVIATIONS.

GCT: Genetic counselling and testing.

NHLS: National Health Laboratory Service.

CHBAH: Chris Hani Baragwanath Academic Hospital.

CMJAH: Charlotte Maxexe Johannesburg Academic Hospital.

SABCHO study: South African Breast Cancer and HIV Outcomes cohort

TP53 mutations: Tumour Protein 53

PTEN gene: Phosphatase and Tensin Homolog deleted on Chromosome 10

SNPs: Single nucleotide polymorphisms

GWAS: genome-wide association studies

HBOC: hereditary breast and ovarian cancers

BRCA1 or BRCA2: breast cancer genes 1 or 2

VUS: Variant of uncertain significance.

DCIS: Ductal carcinoma *in situ*.

ER: Oestrogen receptors

PR: Progesterone receptors

HER2: Human epidermal growth factor 2

FISH test: Fluorescence *in situ* hybridisation

PTT: Protein truncation test

NGS testing: Next-generation sequencing

DECLARATION

I, V Mukendi-Ilunga, declare this dissertation is my own unaided work. It is being submitted for the degree of MMed at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

(Signature of Candidate)

14th day of August 2023 in Johannesburg

ABSTRACT

Genetic counselling and testing can be helpful and enable further management when a carrier is identified early. Mutations in BRCA 1/2 situated on chromosomes 17q21 and 13q12-13 are rare. BRCA 1/2 are tumour suppressor genes essential for preserving genomic integrity, and their mutations will lead to DNA repair deficiency and persistent impaired DNA replication. As a result, dysplasia and breast malignancy will occur.

This study was conducted at Charlotte Maxexe Johannesburg Academic Hospital, the breast unit at Chris Hani Baragwanath Academic Hospital, the Division of Human Genetics at the National Health Laboratory Service and the University of the Witwatersrand.

A total of 498 patients with breast cancer participated in the study. The study population was predominantly black (n=437; 87.75%), with 61 (12.25%) white patients. Most patients were in the 51-60 age group (n=134; 26.91%). There were 80 (16.06%) patients with a known family history of breast/ovarian cancer. Most patients (282; 56.63%) were not eligible for genetic counselling and testing. Of the 216 (43.37%) eligible patients, 39 (18.06%) received genetic counselling, 176 (81.4%) did not, and one (0.46%) refused counselling. All counselled patients received next-generation sequencing testing.

Our findings show that next-generation sequencing is still underused in our health institutions. Most patients were not offered counselling despite meeting the criteria.

Keywords: Genetic testing, invasive breast cancer, BRCA.

Chapter 1

1 INTRODUCTION

1.1 Background and Rationale

In South Africa, invasive breast cancer is a significant public health concern that constitute a heavy burden on both patients and the healthcare system. Breast cancer affects more women t han any other type of cancer and accounts for a sizable portion of all new cancer cases[1]. The prevalence of invasive breast cancer has been rising gradually, emphasising the significance o f developing efficient preventive, early diagnosis, and treatment methods[2]. Several variables c ause the high prevalence of invasive breast cancer in South Africa. These include lack of exercise, unhealthy eating habits, rising obesity rates and lifestyle changes. Additionally, poo rer outcomes are caused by delayed presentation and restricted access to healthcare services i n some areas, which impede prompt diagnosis and starting therapy[3]. The risk of breast cancer is also significantly influenced by genetic factors. Breast cancer risk is considerably enhanced by specific genetic mutations, such as those in the BRCA1 and BRCA2 genes. These mutatio ns are more common in some populations, especially people of Ashkenazi Jewish origin, and can be passed down from parents[4].

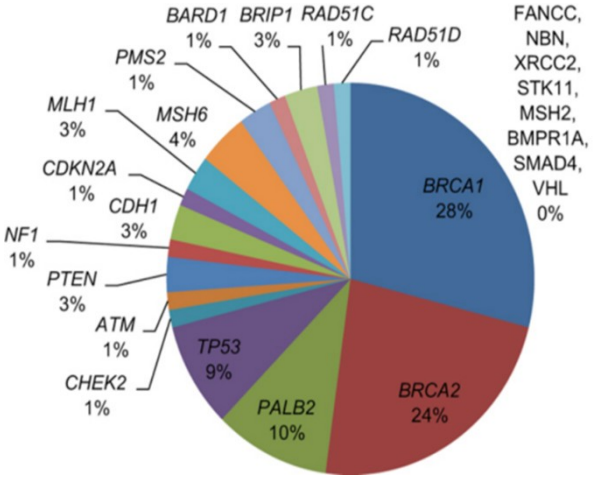

Figure 1: Pie chart of the different genes associated with hereditary 1/2 breast cancer (BRCA1/2)[5].

Invasive breast cancer impacts patients in ways that go beyond their bodily and intellectual he alth. The financial toll of breast cancer is made of direct medical bills, misplaced productivity, and charges for long-term care and assistance services. Given the severity of the issue, invasi ve breast cancer must be thoroughly addressed. This includes establishing efficient preventati ve measures, elevating focus and encouraging early analysis via breast cancer screening pack ages, and ensuring patients diagnosed with invasive breast carcinoma get proper care and assi stance[5]. Developing tailor-made solutions requires intensive knowledge of the precise opport unities and difficulties in South Africa. An essential first step in implementing individualised care and improving the lives of those affected is comparing genetic counselling and experimental strategies used in South African breast devices[6].

Healthcare experts and policymakers can optimise genetic counselling and testing services by identifying gaps in modern practices to produce better management and results for people wit h invasive breast carcinoma. Statistics indicate that the disease's high incidence and occurren ce significantly affect the South African healthcare service[7].

According to South Africa's National Cancer Registry, breast cancer is the most often identifi ed malignancy in women. Recent statistics imply that breast carcinoma accounts for 20% of a ll new cancer diagnoses in South African women. Over the last few decades, invasive breast c ancer occurrence in South Africa has risen substantially[8]. Age-standardised incidence rates of breast cancer grew by approximately 26% among South African women between 2004 and 2 014. This developing trend[9] highlights the need for efficient preventative measures and early detection techniques.

Cities like Johannesburg and Cape Town generally document higher incidence rates than rural areas. However, breast cancer affects women nationally and from all socioeconomic tier s. The frequency of breast cancer in South Africa further emphasises the population-wide impact of the disease. According to a 2017 study, there were around 82 000 prevalent cases o f breast cancer nationally[10].

This highlights the considerable number of women affected by the condition and the resulting problems in supplying them with care and support. It needs to be pointed out that breast canc er does not only affect South African women; men can get breast cancer too, although it is un common and makes up only a small proportion of cases. However, as women account for most breast cancer cases, prevention, analysis, and remedy must be tailor-made to their requirements[11].

The prevalence of invasive breast cancer in South Africa creates the necessity for a standardized approach to this public health issue. Greater knowledge, improved access to heal thcare services, and advanced prevention and treatment strategies can lessen the effects of bre ast cancer and improve the outcomes and quality of life for those affected by the disease. Effe

ctive management and treatment of invasive breast cancers rely significantly on early detection, and accurate diagnosis[12].

Early detection of breast cancer permits early intervention, and increase the likelihood of succ essful therapy. Early detection enables healthcare practitioners to apply curative treatment options, such as surgery, radiation, chemotherapy, and targeted and hormone therapy[13]. Early detection can decrease the risk of metastasis and boost long-term survival by halting the sprea d of cancer to neighbouring lymph nodes or distant organs. Using diagnostic tools like mamm ography, ultrasound, and biopsies clinicians can plan treatment specific to each affected perso n[14].

To decide whether a patient has inherited genetic changes that raise the danger of breast canc er, it is also possible to offer genetic counselling and testing. This allows the patient and any i mpacted family members to receive individualised care and take preventive measures[15]. Over all, early detection and correct diagnosis should be prioritised to improve treatment effectiven ess, decrease morbidity and mortality, and improve the lifestyle of persons with invasive brea st cancer. Genetic factors are generally responsible for the development and spread of breast cancers.[16]

Hereditary gene mutations, which include BRCA1 and BRCA2, are strongly related to a greater risk of breast cancer. These genes contribute to DNA repair and the upkeep of genomi c balance. When these genes are altered, there is a significant increase in the risk of breast ca ncer.[17] Women with BRCA1 mutations have a lifetime risk of as much as 80%, and those wit h BRCA2 mutations have an approximate chance of 45%. TP53 and PTEN are two unusual h ereditary cancer syndromes connected to extra genetic problems that increase the threat of bre ast cancer. The risk of developing breast cancer may also be slightly but cumulatively improv

ed through single nucleotide polymorphisms (SNPs) that have been recognised in more recent research.[18].

Understanding the genetic factors contributing to breast cancers is essential for threat evaluati on, genetic counselling, and tailored prevention and treatment. Genetic testing can help identify at-risk people, allowing them to choose the most appropriate control strategies, dange r-reduction methods, and preventive measures.[18] The biology and disease-associated pathway s can be better understood by researching how genetic factors affect breast cancer. This infor mation can be used to develop new healing goals and specialised treatment plans.[19]

1.2 Problem Statement

In South African breast cancer care, there is a notable disparity between awareness and the im plementation of genetic counseling and testing, despite the increasing recognition of their piv otal role in breast cancer management. Only few studies were assessing the accessibility, avai lability, and use of genetic testing and counselling in this situation.[20] As a result, little is under stood about the strategies used, the extent of identifying affected persons and how much gene tic counselling and testing is integrated into current practice.[21]

Furthermore, little is known about the difficulties and barriers that patients, healthcare worker s, and researchers confront when accessing genetic counselling and testing. There is a lack of evaluation of the genetic counselling and testing supplied to patients with invasive breast carc inoma.[22]

A gap needs to be addressed in the understanding and practice surrounding genetic counsellin g and testing in South African breast units. Existing research revealed a lack of integration an d accessibility of these options amongst South African breast cancer patients, although geneti

c counselling and testing are recognized as crucial factors in breast cancer control.[23] There is a need for increased education and capacity development among healthcare specialists. Ensur ing equitable access to comprehensive genetic evaluation, personalized support, and informed decision-making for individuals at risk of developing invasive breast cancers is imperative. C losing this gap and successfully integrating genetics into breast cancer care is essential for im proving patient outcomes.[24]

Genetic testing and counselling within South African breast units is essential to enhancing pat ient results and supplying individualised care.[25] In addition to ensuring custom-designed inter ventions and treatment plans, this personalised approach fosters patient empowerment and aut onomy. Closing this gap will improve patient-centered care, health outcomes, well-being, and treatment of invasive breast cancer in South Africa.

1.3 Research Objectives

Primary objectives

To determine the percentage of women in the South African Breast Cancer and HIV Outcomes cohort study who fulfil the genetic testing eligibility criteria and would qualify for genetic counselling and testing for hereditary breast and ovarian cancers.[26]

Secondary objectives

- To determine the percentage of women who received genetic counselling.
- To determine what the indication was for genetic counselling.
- To determine the percentage of women who tested positive for a BRCA1 or BRCA2 mutation.

1.4 Significance of the Study

The significance of this work lies in its potential to advance cancer medicine and research in South Africa. The purpose of this study is to evaluate the genetic counselling and testing protocols for patients diagnosed with invasive breast carcinoma in two breast units located in South Africa. The objective is to pinpoint any deficiencies or obstacles in these services and offer constructive suggestions to enhance patient outcomes. By shedding light on the present status of these practices, evidence-based approaches, guidelines, and interventions can be established. Ultimately, this will result in personalized care, informed decision-making, and improved outcomes for individuals affected by invasive breast cancer[27,28].

Incorporating genetics into breast cancer treatment can improve care and well-being for those diagnosed with invasive breast cancer in South Africa. This research has the potential to make a significant impact on breast cancer management in the country.

1.4.1 Scope of the Study

The study will focus on two breast units in South Africa to determine their genetic counselling and testing practices. This approach will allow for a detailed examination of these services in a specific context and make it easier to collect comprehensive evidence.

1.4.2 Assessment of genetic counselling and experiment services

The study evaluated availability, convenience, protocols, patient awareness, and satisfaction with genetic counselling and testing duties for patients diagnosed with invasive breast carcino ma. This appraisal provides insight into current practices and identifies areas for improvement.

1.4.3 Patient perspective

The study incorporates the perspectives of patients who have undergone genetic counselling and testing for invasive breast carcinoma. By including patient experiences and perceptions, t he study aimed to capture a comprehensive understanding of the impact and effectiveness of t hese services from the patient's point of view.

Chapter 2

2 Literature Review

2.1 Overview of Invasive Breast Carcinoma

Breast ductal or lobular cells can develop into an aggressive tumour called an invasive breast cancer. Approximately 80% of all cases of breast cancer fall into this category, making it the most prevalent.[30] The ability of the cancer cells to invade and expand outside the breast tissue into nearby lymph nodes and other organs characterizes this aggressive type of breast cance r.[31] Invasive breast cancer frequently manifests as a palpable breast lump, changes of breast si ze or form, nipple retraction, or skin abnormalities such as dimpling or thickening.[32]

Complex interactions between genetic, hormonal, and environmental variables occur during t he onset and spread of invasive breast cancer. The development of breast cancer is sped up by mutations in particular genes, which are crucial to the disease's aetiology. The most well-kno wn BRCA1 and BRCA2 susceptibility genes are significantly linked to the hereditary breast a nd ovarian cancer syndrome[33]. Certain mutations in deoxyribonucleic acid (DNA) have been linked to a higher likelihood of developing breast cancer.

These genetic modifications affect DNA repair pathways, increasing the risk of breast cancer to 80%.[34] Progesterone and oestrogen also have a significant effect on the development and s pread of invasive breast cancerThe risk of breast malignancy increases with prolonged exposure to estrogen, which can occur due to early onset of menstruation, late menopause, or hormone replacement therapy. Additional risk factors for breast malignancy include alcohol consumption, dense breast tissue, being overweight, and exposure to ionizing radiation.[35,36]

It is crucial to detect breast cancer early to improve prognosis and survival rates. The early detection of breast anomalies is possible through mammography, breast exams, and self-exams.[37] The selection of a treatment plan may be influenced by tumour characteristics, stage, the patient's preferences, and the presence of genetic mutations.[38]

2.2 Genetic Factors and Breast Cancer Risk

Numerous studies have examined how genetic factors may affect a person's risk of developin g breast cancer, and specific gene mutations have been identified as significant contributors t o risk. The best-known genetic defects linked to an elevated risk of breast cancer are BRCA1 and BRCA2 mutations. Women with BRCA1 mutations have a 40-80% chance of developing breast cancer in their lifetime, while those with BRCA2 mutations have roughly a 45% chance.[39] These mutations are commonly found in Ashkenazi Jewish individuals and are inherited in an autosomal dominant manner.[40]

Table 1: Common hereditary syndromes linked to breast cancer

Syndrome	**Gene**	**Related cancers/disease characteristics**	**Inheritance mode**	**Lifetime breast cancer risk**
HBOC	BRCA1, BRCA2	Ovarian, melanoma, breast (M, F), prostate, pancreas	AD	Up to 84%
Li Fraumeni	TP53	Sarcomas, leukaemia, breast, adrenocortical and brain tumours	AD	60%

Cowden Syndrome	PTEN	Breast, thyroid, endometrial, macrocephaly, lipomas, hamartomas	AD	25-50%
Hereditary diffuse, gastric cancer	CDH1	Diffuse gastric cancer, lobular breast cancer	AD	39% (lobular breast cancer)
Peutz-jagers	STK11	GI polyps, pancreas, breast, and sex cord tumours	AD	29%(by age 65)

There are other genetic defects that have been found to increase the risk of breast cancer, apart from BRCA1 and BRCA2. A few cases of breast cancer have been linked to TP53 mutations that are associated with the Li-Fraumeni syndrome. This condition significantly raises the likelihood of developing breast cancer. Additionally, Cowden syndrome has been linked to an increased risk of breast cancer due to mutations in the PTEN gene.[41,42]

According to recent advances in genomic research, single nucleotide polymorphisms (SNPs), which are frequent genetic variations, may increase the chance of getting breast cancer. A minor but cumulative increase in breast cancer susceptibility is caused by these SNPs, which were identified using genome-wide association studies (GWAS).[43] The intricacy of the aetiology of breast cancer is highlighted by the involvement of these SNPs in a wide range of biological processes, including hormone regulation, DNA repair, and cell cycle control.

It is essential to comprehend the genetic factors behind the risk of breast cancer to develop effective therapies. The National Comprehensive Cancer Network advises genetic screening for BRCA1 and BRCA2 mutations for individuals with a significant family history of breast or ovarian cancer or those who meet specific criteria based on their family history and other

risk factors.[44] Identifying these variants paves the way for improved surveillance, risk-reducti on strategies, and specialised treatment options. Genetic counseling is crucial in aiding individuals and families with decision-making and navigating the testing process.[45]

Hereditary factors greatly impact the risk of breast cancer. Families with certain gene mutations, including BRCA1, BRCA2, TP53, and PTEN, are particularly prone to developing the disease. Furthermore, research has unveiled a range of genetic variations that can slowly elevate susceptibility to breast cancer. These findings have significant implications for risk assessment, genetic counseling, and the development of specialized approaches for early detection, prevention, and treatment of breast cancer.

2.3 Genetic Counselling and Testing

Genetic testing and counselling are essential components of treating those at risk for hereditar y breast cancer. Genetic counselling includes reviewing a person's personal and family medic al history to determine the likelihood of a genetic mutation and the associated risk of developi ng breast cancer. The National Society of Genetic Counselors 2021 states that this process hel ps people understand their risk, make informed decisions about genetic testing alternatives, a nd deal with the challenging emotional and moral implications of genetic information.[46]

Genetic testing aims to identify specific gene variants associated with an increased risk of bre ast cancer. Testing that can be done on blood or saliva samples focuses on the BRCA1 and B RCA2 genes and other less common breast cancer risk genes.[47] With the advancement of tech nology, more complete and affordable testing options have been attainable, increasing the acc essibility and availability of genetic testing.

2.4 Genetic Testing Available for HBOCS

Table 2: Available options for genetic testing (private sector in South Africa)[48]

Afrikaner founder screen	**Ashkenazi Jewish founder screen**	**BRCA 1 and BRCA 2 sequencing (SA, local)**	**Multigene panel (international)**
3 variants • *BRCA1* c.2641G>T (p.Glu881Ter) • *BRCA1* c.1374delC (p.Asp458Glufs) • *BRCA2* c.7934delG (p.Arg2645Asnfs)	3 variants • *BRCA1* c.5266dupC (p.Gln1756Profs) • *BRCA1* c.68_69delAG (p.Glu23Valfs) • *BRCA2* c.5946delT (p.Ser1982Argfs)	Sequencing of *BRCA1/2* Genes (>5 000 variants).	Sequencing multiple genes, including BRCA1/2, ATM and CHEK2.

In South Africa, the private sector offers multigene panel tests for HBOC.[49] This strategy has a high identification rate for pathogenic variants. Founder mutation screening is recommended for specific populations, including Afrikaners and Ashkenazi Jews.

Choices regarding the test and results interpretation can be complex (Table 2.2). For individuals with Ashkenazi Jewish or Afrikaner ancestry, founder mutation screening may be a recommended initial test. A founder mutation is a genetic alteration that occurred in a population many years prior and has since remained genetically isolated, potentially due to factors such as geography or religion (such as islanders, Mormons, or Jewish groups).[50] Founder mutations can be either dominant or recessive, and they typically affect adults after they have reached their prime reproductive years. If a founder mutation is dominant, it can spread throughout an isolated population and be passed down from one generation to the next. This can result in a higher prevalence of the mutation within the population than outside of it.

There are over 2000 founder mutations and 3000 established pathogenic variants in the BRCA1/2 genes.[51] Each founder screen tests for only three variants (Table 2). If a woman does not have Jewish or Afrikaner ancestry, it is not recommended for her to use this screening test as a first option. Additionally, if the results of the three founder screens are negative, it is important to offer other testing options, such as complete sequencing for the BRCA1/2 gene.

The gene sequencing for BRCA1/2 is typically done for individuals without Ashkenazi Jewish or Afrikaner heritage. It is a comprehensive method for analysing complete genomes, meaning the whole coding regions of genes are analysed. This test is done by next-generation sequencing (NGS), using parallel sequencing technology to establish the order of nucleotides in the whole genome or selected regions of DNA or RNA, providing ultra-high throughput, scalability and speed.[51]

Multigene panel testing (MGPT) for hereditary cancer predisposition (Table 2.2) is becoming increasingly available. MGPT includes additional genes that may be important for a particular cancer. For example, other genes for breast cancer, besides BRCA1/2, such as CHEK2, PALB2 and ATM, are available locally and tested using an NGS-based approach. MGPT can be helpful for heritable syndromes that include multiple cancers.[52] Performing MGPT may result in detecting variants of uncertain significance (VUSs), particularly if the gene panel selected is larger.

Routinely, laboratories report results such as variants of uncertain significance to permit a regular evaluation and probable re-categorisation built on new findings. A variant of uncertain significance cannot be used in clinical decision-making until it is reclassified because its relationship with cancer risk is uncertain based on present findings. Regarding the public sector, once the patient has met the genetic counselling and testing criteria, they may

be offered a molecular genetic test, considering founder mutations for Afrikaners. Additional genetic testing may be offered if the founder mutation result is negative.

The additional tests include sequencing of BRCA1/2 genes and large rearrangement analysis to identify large deletions and duplications (NGS).[52] There are currently no guidelines for genetic practitioners in deciding whether a founder mutation result is adequate or whether further testing is required after a negative result.

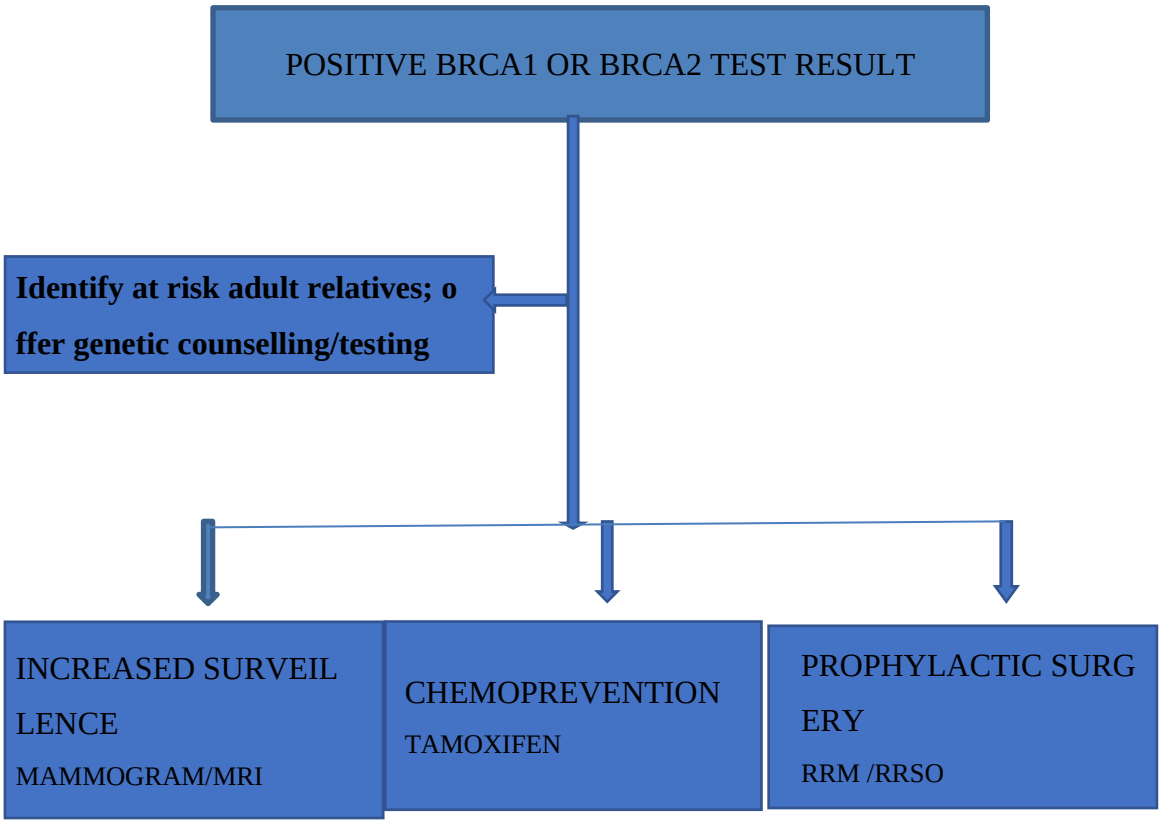

Figure 2: Algorithm after a positive result for BRCA gene.[53]

2.5 Existing Studies on Genetic Counselling and Testing in South African Breast Units

A 2019 study assessed the availability of genetic counseling and testing resources at a public healthcare facility in South Africa.[54] The study found that, regardless of the ease of access to

historical testing functions, there were significant breaks in the provision of genetic counselli ng. This breach included limited access to genetic advisers and a lack of understanding amon g healthcare professionals regarding the appropriate use and interpretation of ancestral test res ults.[55]

In South Africa, a second study was conducted to examine the effects of ancestral testing for hereditary breast and ovarian cancer on women. The study aimed to address issues such as lack of awareness about genetic testing, high levels of anxiety, and challenges in accessing genetic counseling services. The results emphasized the importance of improving support and education methods to enhance genetic counseling and testing for breast cancer patients in South Africa.[57]

In another qualitative study, investigators examined the views of healthcare professionals sup plying genetic counselling and testing services in South Africa.[58] The study found many here dity counselling and testing barriers, such as contradictory methods and advice, inadequate re sources, and time constraints. The study stressed how vital it is to enhance the foundation, ins truction, and support systems for healthcare practioners.[59]

Another study found that, although participants saw heredity counselling and testing as an aid to understanding their risk, there were impediments because of restricted access to genetic studies, protracted waiting periods, and inadequate follow-up. The study emphasised the need for upgraded service delivery and money to accommodate the increasing demand for genetic counselling and testing in South Africa.[60]

A study investigated the challenges that South African daughters with a family history of breast and ovarian cancer face when it comes to genetic testing. The study found that there are various obstacles, including financial limitations, lack of knowledge and understanding about genetic testing, cultural beliefs and scepticism about genetics and cancer[61]. The study st

ressed how important it is to erase these barriers to increase the approach to appropriate care and promote genetic testing.[62]

Another study looked at a systematic assessment of the brochure on genetic counselling and testing for hereditary breast and ovarian cancer in South Africa.[63] The evaluation accentuated the dearth of research in this area and labelled information breaches concerning the results of genetic experiments, counselling, and maintenance. The authors emphasised the need for mor e studies to develop culturally appropriate interventions and standards for ancestral testing an d counselling and to position the unique challenges found in South Africa.[64]

Research indicates a need for better awareness of, approach to, and education on genetic testing and counselling businesses. Addressing the challenges and difficulties South African p atients and healthcare professionals face is also essential. Additional study is necessary to eva luate patient outcomes, explore current practices, and create methods to enhance genetic testing and counselling in South African breast units[65].

2.6 Research Gaps and Rationale for the Current Study

In reviewing genetic counselling and testing for patients in South African breast units diagnos ed with invasive breast cancer, the current study closes various research gaps. Although there haven’t been many in-depth analyses of these services for invasive breast cancer, studies alre ady carried out in South Africa have illuminated the challenges and barriers surrounding gene tic testing and counselling. The protocols, patient perception and satisfaction, accessibility, an d availability of genetic testing and counselling in South African breast units have also receiv ed minimal research attention. The current study aimed to fill these gaps by conducting a thor ough examination of genetic counselling and testing procedures in two South African breast u nits.

Our goal is to improve patient outcomes for invasive breast cancer in South Africa by evaluating genetic counseling and testing procedures. By identifying gaps and challenges, we hope to inform evidence-based strategies that could enhance the delivery of these services and lead to better patient care and treatment outcomes.[67]

Chapter 3

3 Methods

The methods and techniques used to study genetic counselling and testing of patients with inv asive breast cancers in two South African breast units are defined in this chapter. The study's layout, participant selection, statistics series strategies, and moral issues are all described.

3.1 Research Design

The study used retrospective qualitative and quantitative procedures in a mixed-methods appr oach. The process of genetic counselling and testing for people with invasive breast cancer in South African breast clinics was thoroughly investigated using this design. In-depth scrutiny of patients' information with genetic counsellors and healthcare professionals was conducted as part of the qualitative component to learn more about their perspectives, issues, and experi ences. On the quantitative side, it was determined how frequently genetic testing was used an d how this affected treatment choices by methodically analysing patient data and medical rec ords. The complicated interactions between genetic testing, counselling, and breast cancer tre atment in the South African healthcare setting were made easier to comprehend with the help of this dual-method approach.

3.2 Participants and Sampling

Participants:

In total, 498 people with invasive breast cancer who were dealt with at a breast unit in South Africa participated in the project. This sample size helped to provide a significant representati on of the affected person population.

Sampling:

To ensure a comprehensive representation of participants, a purposive sampling strategy was employed. The inclusion criteria targeted women with primary invasive breast cancer on the histology. The exclusion criteria were patients with ductal carcinoma *in situ*, benign breast disease, age under 18 years old, significant cognitive deficit, and a history of cancer diagnosis (besides non-melanoma skin cancer or cervical carcinoma *in situ*). This approach made it possible to choose patients who fit the stated requirements and could provide insight into the process of genetic counselling and testing. The observer sought to gain a complete picture of t he difficulties and advantages associated with genetic counselling and testing in the setting of invasive breast cancer by careful consideration of the genetic testing eligibility criteria for women with a personal history of breast/ovarian cancer in the government system in Johannesburg, South Africa, as stated by the National Health Laboratory Service as follows:

1. Family history of a known mutation in a cancer predisposition gene (e.g., BRCA 1/2, PTEN, p53).
2. Personal history of breast cancer diagnosed before the age of 50.
3. Cancer diagnosed before the age of 60 (ovarian cancer).
4. Two contralateral primary breast cancers at any age.

5. One or more close relatives with cancer of the breast < 50 years old.
6. One or more close relatives identified with ovarian cancer.
7. Two or more close relatives identified with cancer of the breast or pancreas with at least one < 60 years old.
8. Ashkenazi (eastern European) Jewish ancestry.
9. One or more family members with male breast cancer.
10. Personal history of triple-negative breast cancer

3.3 Data Collection

We used two datasheets in the study. The first contains the study and folder numbers, and the second de-identified demographics, tumour biology and genetic parameters. The statistics focused on all participants who met the NHLS eligibility criteria for genetic counselling and testing to gain information on the method at two South African breast units. All patients enrolled in the South African Breast Cancer and HIV Outcomes cohort study were studied according to the above criteria. Eligible patients were identified, and their genetic counselling records in the Division of Human Genetics at the NHLS were searched to determine whether the participant had received genetic counselling, testing or both. Files and test results from the NHLS were accessed and analysed. Eligible individuals were divided into those who received counselling and testing versus those who did not. Those who received genetic testing were categorised either positive, negative or with a variant of uncertain significance. The review included patients from 1 July 2015 to 30 March 2019.

The collection method was carefully planned to protect participant privacy and confidentialit y. Ethics were of utmost importance throughout the information-gathering phase to recognise contributors' rights to privacy.

3.4 Data Analysis:

Stata version 14 (StataCorp Limited, Texas, United States of America) was used for data analysis. Descriptive statistics to describe the distribution of patients according to gender, age, race, the total number of patients who met the genetic eligibility criteria for counselling and testing in the South African breast cancer and HIV outcomes cohort study databases, the overall number who underwent counselling and testing and the total number of patients who were tested positive for BRCA mutations was calculated. Normally distributed data were represented as mean (standard deviation). Comparisons were made using Pearson's Chi-squared test or Fisher's exact test where relevant. Statistical tests were two-sided, and $p<0.05$ was viewed as significant.

3.5 Sources of Bias

Bias was expected to be minimal as the study was a retrospective audit. Possible bias from incomplete or missing information was minimised by thorough data review and all accessible information.

3.6 Ethical Considerations

Our research is a sub-study of the South African Breast Cancer and HIV Outcomes study. Ethical approval was received from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (clearance certificate M1911207). In addition, permission to do the research was obtained from the research review boards of Charlotte Maxexe

Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital, the Human Resource Department, the Head of the Department of Human Genetics at the National Health Laboratory Services in Johannesburg and the chief executive officers and the study co-ordinator of South African Breast Cancer and HIV Outcomes. The study was conducted according to the principles of the Declaration of Helsinki. The result of the research will be made accessible to the National and Provincial Departments of Health, the Department of Surgery at Wits University, and the Departments of Surgery at participating hospitals. It will also be presented at academic conferences and submitted for publication by peer review.

Chapter 4

4 Results

4.1 Patient Demographics

Table 3: Demographic characteristics of the patients

Variables	Total	CHBAH n (%)	CMJAH n (%)	p-value
Age Mean (SD)	54.74 (13.15)	56.38 (13.8)	53.1 (12.3)	0.0053
Age groups				
23-40	72 (14.46)	27 (10.84)	45 (18.07)	
41-50	131 (26.31)	68 (27.31)	63 (25.3)	0.005
51-60	134 (26.91)	61 (24.5)	73 (29.32)	
61-70	92 (18.47)	46 (18.47)	46 (18.47)	
71-98	69 (13.86)	47 (18.88)	22 (8.84)	
Race				
Black	437 (87.75)	244 (97.99)	193 (77.51)	<0.001
White	61 (12.25)	5 (2.01)	56 (22.49)	

Most patients were between 51-60 years (n=134; 26.91%) and 41-50 years (26.31%).

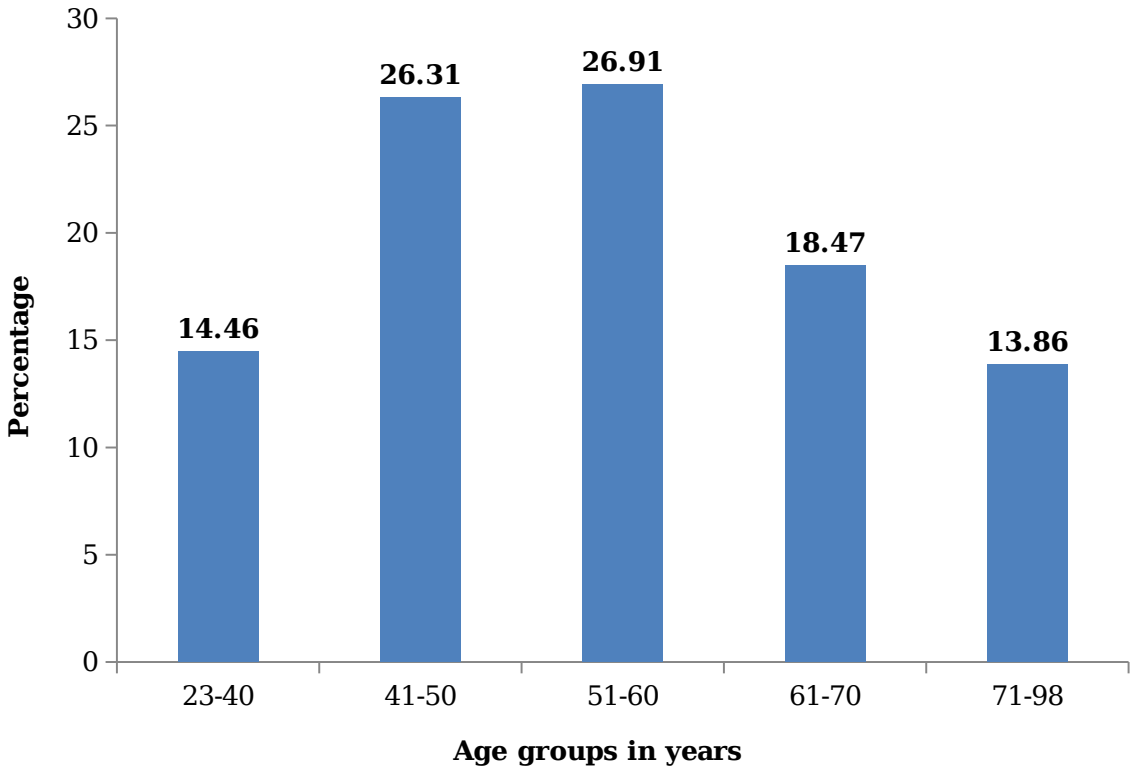

Figure 3: Age group distribution in years of breast cancer patients. The highest percentage age group was 51-60 years, and the lowest was 71-98 years. The mean age was 54.74 (13.15) years.

4.2 Cancer-Related Clinical Characteristics Among Breast Cancer Patients

Table 4: Clinical characteristics of the patients

Variable	**Categorical variable**	**Frequency n(%)**
Genetic mutation carrier in the family	Known Unknown	0 498 (100.0)
Family history of breast/ovarian carcinoma	Known Unknown	80 (16.06) 418 (83.94)
Tumour immunohistochemistry	ER, PR and HER2 negative Yes No Ki67 <20 >20	 78 (15.66) 420 (84.34) 184 (36.95) 314 (63.05)
Age of cancer onset	<50 years ≥50 years	188 (37.75) 310 (62.25)

None of the patients knew about a genetic mutation carrier in the family. Regarding the tumour immunohistochemistry, there were 15.66% (n=78) ER, PR and HER2 triple-negative patients. Thirty-seven per cent of patients were younger or middle-aged (49 years and younger).

4.3 Cancer-Related Family Characteristics Among Women with Breast Cancer.

Table 5: Relationship between a breast cancer patient and a person with a history of breast/ovarian cancer.

Degree class	**Relationship**	**Frequency (%)**
First degree relatives	Mother	69 (12.75)
	Father	6 (1.25)
	Sister	87 (17.5)
	Brother	6 (1.25)
	Daughter	12 (2.5)
	Overall	180 (35.9)
Second-degree relatives	Grandmother	50 (10.0)
	Uncle	6 (1.25)
	Aunt	93 (18.75)
	Niece	13 (2.5)
	Cousin	19 (3.75)
	Overall	181(36.3)
Not specified		137 (27.5)

Of 80 women with a history of breast/ovarian carcinoma, 14 (18.75%) indicated that the family member was an aunt, and 11(17.5%) said the family member was a sister.

4.4 Genetic Counselling and Testing Uptake

Figure 4: Genetic testing process flow chart from eligibility and counselling to testing. The study enrolled 498 patients, and 87.18% underwent genetic testing. Most patients who received genetic counselling also accepted testing. Only a small number of patients were offered genetic counselling. However, the study also indicated that most of those who were counselled had genetic testing.

4.5 Genetic Testing Outcome.

Table 6: Genetic testing-related factors among breast cancer patients (n=34)

Variable	**Categorical variable**	**Frequency**	**Percentage**
Laboratory testing Founder mutations	Yes No	8 26	23.53 76
Laboratory screening	Protein Truncation Test Next-Generation Sequencing)	0 34	0 100
Genetic testing results	BRCA1 BRCA2 Negative VUS Unknown	2 4 18 3 7	5.88 11.76 52.94 8.82 20.58
The communication channel of results to patients	Telephonically In-person counselling session No response from the patients Unspecified	8 13 1 12	23.24 38.24 2.94 35.29

Altogether, 34 women underwent genetic testing. None of the patients had the Protein Truncation Test laboratory screening. Most results were communicated via counselling sessions (n=13; 38.24%), while 23.34% (n=8) got their results telephonically. There were 12 (35.29%) whose genetic results communication channel was not specified. The majority of the patients had negative genetic testing results (n=18; 52.94%), 5.88% (n=2) had BRCA1, and 11.76% (n=4) had BRCA2. There were 8.82% (n=3) patients with VUS, and five (14.7%) results were unknown (not found in the data system).

Chapter 5

5 Discussion

This retrospective cohort study in our two public sector breast units focused on the efficiency of implementing genetic counselling and testing in Johannesburg. The result of the audit regarding patient demographics and cancer-related clinical characteristics among breast cancer patients is given in Tables 3 and 4. Figure 4 and Table 6 summarise genetic counselling, testing uptake, and testing outcomes.

We found BRCA 1 mutations in two patients and BRCA 2 mutations in 4 patients, what results in a detection rate of 5.88% and 11.76%. This is similar to other international studies, which reported a prevalence of BRCA mutation between 5 and 10%.[68,69] In Italy, the BRCA detection rate was reported to be 6.4%[70], and a study published in 2020 by the American Journal of Surgery also reported the detection rate to be 6.%.[71] Expanded genetic testing is now available in the public sector in South Africa, offering an eight-gene panel. In the future, we expect to see increased diagnostic yield with genetic testing. Our data show a higher prevalence of breast cancer in women in their 50s. These findings correspond with results reported elsewhere about women from low-to-middle-income countries.[72]

There is a need to emphasise regular awareness about breast cancer, especially in young and middle-aged women. Awareness must be emphasised in hospitals, clinics, schools, workplaces, public gatherings and symposiums. How and who will support this awareness programme will require a multisectoral approach.

For example, in Johannesburg, South Africa, some private organisations have been involved in the breast cancer programmes at CHBAH and CMJAH for some years.

A multidisciplinary approach in the programme has demonstrated access benefits for genetic testing and has resulted in a high detection rate (14.9%) for common mutations, as stipulated in the literature.[73]

Regarding hereditary breast cancer in our population, the level of awareness and challenges in detecting affected family members is enabled at this stage by testing only common mutations. This is less expensive than multigene panel testing for hereditary breast and ovarian cancers. This strategy has been shown to have a significant identification rate of pathogenic variants, and interpreting results is easy. Our study also found more black than white women with breast cancer, which reflects the SA population.

The above findings may assist in terms of resource distribution during the implementation of breast cancer programmes, especially in different SA population groups.

We conducted an audit to assess our patients' awareness of the genetic mutation carriers in their families. None of the patients had any knowledge of such carriers. We are concerned about the lack of awareness among patients about the genetic aspect of breast cancer. This shows the need to emphasise GCT in our community. We believe this particular situation could be explained by the fact that the number of trained genetic counsellors is still small. For example, at the two breast units, only two genetic professionals could support the service and genetic counselling and testing was only available once a month.

Clearly, it shows these individuals were under pressure, and the possibility of missing some information was considerable. Our data suggest that many patients had a family history of breast/ovarian cancer, but most were not offered genetic counselling. Again, this was a significant concern, and a possible explanation could still be related to the number of healthcare providers, resulting in slow service delivery.

We suggest that an important activity, such as a breast unit, needs much more support, especially when international statistics show that breast cancer is the most common cancer affecting women globally.[74]

We also found that, due to emotional factors, one patient declined GCT after receiving her result. However, our main concern was to elucidate the significance of the factors associated with the possible refusal of GCT. This was an important finding related to psychosocial harm after receiving a positive result, which has also been reported elsewhere in the world.[75]

We could not determine how soon the GCT was done following the diagnosis. Also, this aspect raised a discussion about choosing the appropriate time to provide genetic counselling and testing when the breast cancer diagnosis has been made. Such direction will help minimise psychosocial harm to patients. However, there is evidence that the benefit of tailoring surgery and adjuvant treatment can mitigate the psychosocial implications.[76]

Regarding the result communication channel, most were communicated telephonically, and a few were via counselling sessions. As we all know, making a patient aware of her breast cancer diagnosis is always demoralising. The question remains whether the results should be delivered telephonically or via in-person counselling sessions. We suggest that results should

be given during counselling sessions. In this case, the healthcare professional can provide physical and mental support. We were unable to assess the psychological impact when results were delivered telephonically.

Despite the small number of patients who had genetic counselling and testing, the detection rate of BRCA1 and BRCA2 mutations was still the same as that reported globally between 5% and 10%.[77] With the implementation of additional genetic counselling clinics and expanded genetic testing, we expect more patients with hereditary cancer syndromes will be detected and can benefit from tailored management.

Chapter 6

6 Practical and Clinical Implications

Healthcare experts, decision-makers, and researchers working in genetic counselling and testi ng for invasive breast cancer can all gain from understanding the sensible and scientific impli cations of this research. The findings offer realistic guidelines for enhancing affected person c are, genetic counselling methods, and dealing with humans with breast cancer.

Firstly, the location variations in the use of genetic counselling and the effects of testing amo ng numerous demographic populations spotlight the significance of customising outreach and educational applications. Clinicians should use focused efforts to elevate recognition and und erstanding amongst underprivileged people for equal rights of entry to genetic counselling ser vices and healthcare. These efforts could include community seminars, instructional materials, and culturally applicable discussions.

The participants' emotional and psychological issues additionally emphasise the cost of prese nting thorough pre- and publish-take a look at counselling. To assist patients in making educated decisions, genetic counsellors need to have open discussions with them about the possible psychological outcomes of testing. It may be important to offer psychological help a nd access to mental health specialists to reduce fear and emotional discomfort and ensure suff erers are prepared for the consequences of their genetic testing.

In the context of invasive breast cancers, the realistic and clinical implications of testing spotl ight the significance of an affected person-centred and inclusive technique to genetic counsell ing and testing.

Healthcare systems can enable humans to make knowledgeable selections, negotiate capabilit y boundaries, and maximise their general breast cancer care journey by addressing inequities in uptake, offering thorough psychological support, and adapting counselling to gender-specif ic concerns. These implications highlight the incorporating genetic testing and counselling int o a complete, patient-centred approach to coping with breast cancer.

CHAPTER 7

7 Conclusion and Study Limitations

To sum up, this study sheds light on the complex interplay between patient perspectives, dem ographic factors, and clinical outcomes in the challenging field of genetic counseling and testi ng for invasive breast cancers. The findings emphasize the importance of personalized and pa tient-centered approaches, as well as improving the quality of care.

The results of this study highlight the need for equitable access, comprehensive pre-research on counseling, and psychological support to meet the diverse emotional and informational ne eds of individuals when genetic counseling becomes a crucial part of managing breast cancer. By applying these insights, healthcare systems can develop a more inclusive and effective fra mework for genetic counseling, leading to better patient outcomes, informed decision-making and better navigation of the complexities of invasive breast cancers. However, our study has some limitations, such as unspecified genetic results and missing biomarkers and immunohist ochemistry in patient files, which made analysis challenging.

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