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Genetic testing for inherited cancers in patients within the private healthcare sector of South

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Genetic Testing for Inherited Cancers in Patients within the Private Healthcare Sector of South Africa

Tasmyn Dale Scriven

A research report (in the format of a "submissible paper") submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements of the degree of Master of Science in Medicine (Genetic Counselling)

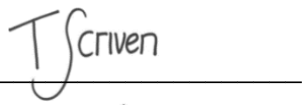
Johannesburg, 2021

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Declaration

I, Tasmyn Dale Scriven, declare that this research report (in the format of a "submissible paper"), is my own, unaided work. It is being submitted for the degree of Master of Science in Medicine (Genetic Counselling) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



28 February 2022, in Johannesburg

Contribution of the Candidate to this Paper:

Declaration: Student's contribution to article and agreement of co-authors

I, Tasmyn Dale Scriven, student number 1345387, declare that this Research Report is my own work and that I contributed significantly towards research findings presented in the paper intended for publication below.

Signature of student:  Date: 28 February 2022

Name of Supervisor 1: Dr. Shelley Macaulay

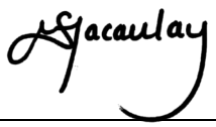
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Agreement of Co-Authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Research Report.

Article Title: Genetic Testing for Inherited Cancers in Patients within the Private Healthcare Sector of South Africa

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Author 1	Tasmyn Scriven		28 February 2022
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Dedication

This research report is dedicated to Timothy, Mom and Dad for their love, support and encouragement to go on every adventure, including this one.

Abstract

Introduction: Inherited cancer syndromes are responsible for approximately 13.5% of all cancers. They are caused by germline mutations in cancer susceptibility genes which are passed down from generation to generation. The development and application of Next Generation Sequencing technologies, such as gene panels, has increased the accuracy, efficacy and affordability of identifying patients who have, or are at increased risk of, hereditary cancer syndromes. These individuals have the opportunity to pursue tailored treatment strategies as well as surveillance and risk-reducing surgeries in order to reduce cancer-related morbidity and mortality. Despite the benefits of knowing one's genetic status, medical aid schemes in South Africa do not reimburse patients for international genetic testing which is more broad, affordable and has a quicker turn-around time.

Aims: The aim of this study was to provide insight into the utilization of genetic counselling and the uptake of genetic testing through the Division of Human Genetics, National Health Laboratory Service and University of the Witwatersrand, Johannesburg.

Methods: A total of 290 files of patients who attended a genetic counselling session for a personal and/or family history of cancer during the study period were assessed.

Results and Discussion: The mean (standard deviation) age of the patients was 47 ± 14.4 years and 54.1% (157/290) were from a high-risk population group with Ashkenazi Jewish and/or Afrikaner ancestry. A total of 46.2% (134/290) had both a personal and family history of cancer. The uptake of genetic testing was 71.0% (206/290) and patients with and without a family history of cancer were just as likely to pursue genetic testing (p=0.195). A total of 37.4% of tests were conducted overseas and most medical aids do not pay for international testing. International genetic testing is more cost effective and has a faster turn-around time, thereby affording individuals the opportunity to early interventions to reduce cancer incidence. Gene mutations in cancer susceptibility genes were found in 24.3% (50/206) of these individuals.

Conclusion: This study showed that the identification of gene mutations causative of an inherited cancer syndrome over a six-year period has allowed 24.3% of individuals the opportunity to pursue increased surveillance and risk-reducing management that could decrease the cancer burden in themselves and their families. These findings highlight the necessity for medical aids to expand their coverage to include international genetic testing as the implementation of cancer screening and risk reducing measures would be a more cost effective approach than the long term management and treatment of a cancer diagnosis.

Acknowledgements

Firstly, I would like to thank my supervisors Dr. Shelley Macaulay and Ms. Marianne Gomes for their continuous support as well as their guidance in formulating the research and methodology thereof. Their insight in inherited cancer syndromes inspired this project as well as my own passion for cancer genetic counselling. I have appreciated their engagement and keen interest in this research project as well as my own growth in the genetic counselling and research field.

I would also like to thank the genetic counsellors at the Division of Human Genetics, Clinical and Counselling Section, National Health Laboratory Service and University of the Witwatersrand for their continuous support and friendly atmosphere.

A special thank you to my fellow genetic counselling student, Zandisiwe Goliath, genetic counselling intern, Sydney Francois, and genetic counsellor, Monica Araujo for their motivation and their friendship over the last two years.

Lastly, I would also like to thank my family and friends for the support, love, enthusiasm and opportunities that they have given me.

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List of Abbreviations

ADP	Adenosine diphosphate
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
e.g.	for example
etc.	etcetera
et al	and others
GLOBOCAN	Global Cancer Observatory
HBOCS	hereditary breast and ovarian cancer syndrome
IQR	Interquartile Range
MRI	Magnetic Resonance Imaging
n	Absolute number
NHLS	National Health Laboratory Service
PARP	poly-ADP ribose polymerase
PGT	Preimplantation Genetic Testing
$PREMM_5$	Prediction Model for gene Mutations
SD	Standard Deviation
UK	United Kingdom
USD	United States Dollar
VUS	Variant of Uncertain Significance
WITS	University of Witwatersrand
ZAR	South African Rand
%	Percentage

Research Report in the Format of a Submissible Paper

This work has been written up as a paper for submission to the Journal of Familial Cancer. The author guidelines, including word count of abstract, and referencing style have been adhered to and are included in the appendix. However, tables and figures have been inserted in text for ease of reference.

Genetic Testing for Inherited Cancers in Patients within the Private Healthcare Sector of South Africa

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Abstract for Paper Submission

Inherited cancer syndromes are responsible for approximately 13.5% of all cancers. The development and application of multigene panels has increased the efficacy and affordability of identifying patients who have, or are at increased risk of, hereditary cancer syndromes. Despite the benefits of knowing one's genetic status, medical aid schemes in South Africa do not reimburse patients for international genetic testing. The aim of this study was to provide insight into the utilization of genetic counselling and the uptake of genetic testing through the Division of Human Genetics, National Health Laboratory Service and University of the Witwatersrand, Johannesburg. A total of 290 patient files were assessed. The mean (standard deviation) age of the patients was 47 ± 14.4 years and a total of 134/290 (46.2%) had a personal and family history of cancer. The uptake of genetic testing was 71.0% (206/290) and a total of 77/206 (37.4%) of these tests were conducted overseas and were not covered by medical aid schemes. Gene mutations in cancer susceptibility genes were found in 24.3% (50/206) of these patients. International genetic testing is more cost effective and has a faster turn-around time, thereby affording certain patients the opportunity to pursue early interventions to decrease the cancer burden in themselves and their families. These findings highlight the necessity for medical aids to expand their coverage to include international genetic testing as the implementation of cancer screening and risk reducing measures would be a more cost effective approach than the long term management and treatment of a cancer diagnosis.

Introduction

Germline mutations in cancer susceptibility genes are observed in up to 13.5% of all patients with cancer and are associated with an increased risk of developing certain types of cancer [1] There are certain features that characterise hereditary cancer syndromes and these features are often utilised as clinical clues that point towards an inherited cancer syndrome within a family. These clinical clues include cancer occurring at an early age of onset (e.g. before 50 years of age for breast and colon cancer, before 60 years of age for ovarian cancer), the diagnosis of bilateral cancer, clustering of linked cancers in one family (e.g. breast and ovarian cancer, colon and endometrial cancer), multiple family members affected with the same, or closely related, cancers, multiple affected generations, the presence of rare cancers such as a male breast cancer, and a family descending from a particular ethnic group that has a high incidence of hereditary cancer due to founder effects (e.g. the Ashkenazi Jewish population and the Afrikaner population) [1, 2]. The South African Afrikaner population originated from a group of European settlers (predominantly of Dutch, German and French ancestry) who settled in the Western Cape Province of South Africa in the 17th century. This gave rise to a founder effect whereby genetic mutations present in the original group of individuals increased in frequency over time, three of which are in the *BRCA* genes causing a predisposition to breast and ovarian cancer [3]. Genetic testing may be offered to families where an inherited cancer syndrome is suspected to refine their risks of having a germline mutation in a cancer susceptibility gene [4].

Genetic testing has shifted from sequencing one gene at a time to testing several genes simultaneously due to the development of Next Generation Sequencing (NGS) technology [5]. In the past, testing was limited to sequencing of the *BRCA1* and *BRCA2* genes that cause hereditary breast and ovarian cancer syndrome (HBOCS) and founder *BRCA* mutation analysis for patients of Afrikaner and Ashkenazi Jewish ancestry. There are three founder Ashkenazi Jewish *BRCA* mutations and three founder Afrikaner *BRCA* mutations [3]. Hereditary cancer syndromes and their associated phenotypes have considerable overlap in presentation and associated malignancies. For example, ovarian cancer is a common manifestation of mutations in genes associated with HBOCS as well as Lynch syndrome [6]. Multigene panels have the ability to test multiple genes associated with a predisposition to a specific cancer simultaneously [2]. For example, a multigene panel can identify variants in high penetrance genes such as *BRCA1* and *BRCA2* that are associated with HBOCS, mismatch repair genes associated with Lynch syndrome, as well as *CDH1, PTEN, STK11* and *TP53* genes that are associated with

hereditary diffuse gastric cancer, Cowden syndrome, Peutz-Jaghers syndrome and Li-Fraumeni syndrome, respectively, in one test [6, 7].

The identification of a germline genetic mutation in an individual has many clinical implications such as the opportunity to undergo risk-reducing interventions, be candidates for precision medicine and enrolment in clinical trials [1]. They can also undergo cancer screening more frequently with more sensitive technologies [8]. This is particularly the case for inherited cancer syndromes that cause a predisposition to breast cancer. In South Africa, population screening for breast cancer starts at 40 years of age. However, when there is a family history of breast cancer, screening should start five years prior to the youngest diagnosis of breast cancer [9]. Furthermore, an annual breast MRI is recommended for at-risk individuals who are younger than 30 years, after which a mammogram is recommended [9]. These medical interventions, that reduce the risk of cancer and assist in earlier cancer detection, can be extended to at-risk family members if they choose to undergo cascade testing (the process of counselling and testing at-risk family members for a familial mutation) [1]. Additionally, genetic test results can be utilised for reproductive decision making and allow families to consider prenatal testing or assisted reproduction strategies, including donor gametes or preimplantation genetic testing (PGT), as well as adoption [10]. Genetic counsellors are essential in determining who is at risk for an inherited cancer syndrome and would, therefore, benefit from genetic testing for inherited cancer syndromes [11]. Additionally, genetic counsellors play an important role in the genomic era in providing pre and post-test counselling and the discussion of variants of uncertain significance (VUS) [12].

The National Society of Genetic Counselors describes genetic counselling as “the process of helping people understand and adapt to medical, psychological, and familial implications of genetic contributions to disease” [13]. Genetic counsellors are uniquely trained medical professionals who are able to explain the clinical and genetic aspects of a cancer diagnosis, or a suspected inherited cancer syndrome, to an individual in a comprehensive manner. Genetic counsellors provide information about the genetic aetiology of cancer, the likely inherited cancer syndrome, the mode of inheritance, possible family members who may be at risk, the benefits and limitations of genetic testing and lastly, recommendations for management, surveillance and prevention [6]. Additionally, genetic counsellors offer the most appropriate genetic tests for whichever inherited cancer syndrome they are suspecting. Genetic counsellors also use their knowledge and the family pedigree to determine who the most appropriate individual in a family is to test, as well as the most appropriate genetic test to offer. Ideally, a

person who is/has been diagnosed with cancer should be tested first. When an unaffected individual undergoes genetic testing first and tests negative, this does not refute an inherited cancer syndrome in the family. Genetic counsellors ensure that patients feel supported and capable of making informed decisions based on their healthcare needs and personal beliefs and values, as well as ensuring that patients have the capacity to cope with the emotional implications of a hereditary cancer diagnosis [14].

Risk assessments are an integral part of genetic counselling as they provide individualised predictions as to whether or not an individual may carry a genetic mutation causative of an inherited cancer syndrome. Genetic counsellors at the NHLS/WITS perform a manual risk assessment that combines assessing the genetic, familial and oncological factors to quantify the likelihood of detecting a mutation in an individual [11, 15]. In addition to the risk assessment, genetic counsellors use their knowledge and the family pedigree to determine who the most appropriate individual in a family is to test, and the most appropriate genetic test to offer. Individuals who receive a high risk assessment from a genetic specialist tend to fulfil a large proportion of the features that characterise an inherited cancer syndrome [16]. Individuals who do not fulfil any criteria for an inherited cancer syndrome are regarded as low risk. Those who fulfil some criteria of an inherited cancer syndrome are said to be at moderate risk [16]. Manual risk assessments are sometimes used in conjunction with computerised risk models that have been validated and are used to determine the likelihood of identifying a genetic mutation in an individual [17]. These online risk assessment models include CanRisk (formerly BOADICEA) which calculates the probability of detecting a genetic mutation in genes such as *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*. *ATM*, *RAD51D*, *RAD51C* or *BRIP1*[18]. Similarly, PREMM$_5$ is an online prediction model that estimates the probability of an individual carrying a germline mutation in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes causative of Lynch syndrome [19]. A probability score of ≥ 5% is indicative that genetic testing for Lynch syndrome should be offered [19]. Both CanRisk and PREMM$_5$ are online prediction models that take personal and family history of cancer into account. The models consider factors such as demographic data (current age and sex) as well as types of cancer in the family and ages of at diagnoses. The software then estimates a probability score of detecting a genetic mutation in an individual based on these factors. One of the major limitations of these computational models is that they were designed for use in largely European populations and their application in other populations, such as the South African population, has not yet been determined. Additionally, CanRisk and PREMM$_5$ are specific to HBOCS and Lynch syndrome respectively, and therefore

exclude a multitude of other inherited cancer syndromes for which no computational risk models have been designed.

In countries such as the United Kingdom (UK), risk models such as the Manchester Scoring System is used as a strict measure to determine whether patients are eligible for genetic testing [9, 17]. The Manchester Scoring System is a point-based system that assigns points according to personal and family history of cancers that are associated with hereditary breast and ovarian cancer syndrome. The factors that this scoring system takes into account include the type of cancers, the age of cancer diagnosis as well as the pathology of the relevant cancers [9, 17]. Those that score 15-20 points using the Manchester Scoring System, based on their personal and family history, have a 10-20% likelihood of detecting a mutation in *BRCA1/2* and are eligible for genetic testing [9]. However, these risk models were designed for use in largely European populations and their application in other population groups has not yet been determined. While risk models may reduce inappropriate testing, many individuals who may be harbouring a genetic mutation are overlooked because they do not fit criteria. As such, private patients in our setting including those who are at a low, or low to moderate risk of having an inherited cancer syndrome, have the option to pursue genetic testing. There have been no studies in South Africa that have compared the accuracy of manual risk assessments, to the online risk prediction models.

In South Africa, socioeconomic status is one of the highest contributors to inequitable access to healthcare [20]. Only approximately 16% of the population has access to private medical aid and is therefore able to attend private hospitals. Individuals with access to private medical aid, or with the ability to pay for private healthcare and those with a sustainable household wealth are referred to as "private patients" and are, in general, more likely to have access to more extensive genetic testing as they are able to cover the cost of the test themselves [20].These patients have the opportunity to have genetic testing at local private laboratories as well as international laboratories. Gene panels offered at local laboratories cost approximately USD 760 (equivalent to ZAR 11 000) for the evaluation of approximately ten genes whereas international gene panels are more extensive (more than 200 genes) and are more affordable costing approximately USD 250 which is equivalent to ZAR 3 700 [22] (cost estimates as of October 2021). However, medical aid schemes do not reimburse patients for international genetic testing and these patients have to pay out of their own pocket. In most cases, despite local testing being more expensive, medical aid covers at least some of the local genetic testing costs, however, it is usually deducted from an individual's medical savings account. There are

a multitude of medical aid schemes in South Africa and each medical aid scheme has different plans depending on what procedures an individual wants covered, and what they are able to afford. Each medical aid scheme will differ in terms of whether they will reimburse their clients for genetic testing and also for screening procedures.

The aim of this study was to provide insight into the utilisation of genetic counselling and the uptake of genetic testing for inherited cancer syndromes in the private healthcare sector, Johannesburg, South Africa.

Methods

Ethical Clearance was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (WITS) (Ethics clearance certificate: M210272) (*Appendix A*)

Patients and Setting

The study population included private patients who were seen only by genetic counsellors and medical geneticists from the Division of Human Genetics, WITS and the National Laboratory Service (NHLS) for a personal and/or family history of cancer during the period of 2015 to 2020. Eligible participants were individuals who were older than 18 years of age who, if they did pursue genetic testing, only pursued genetic testing through the Division of Human Genetics, WITS and the National Laboratory Service (NHLS). The Division of Human Genetics, WITS and the NHLS, keeps a file for each patient seen by the staff of the Clinical Section according to their diagnosis. This study was a retrospective file review of private patients who were seen for an initial cancer genetic counselling consultation.

Data Collection

The following data were retrieved from patients' genetic files: demographic information (age, sex, ethnicity, etc.), the type of cancer(s) present in the referred individual and his/her family members using the patients' family pedigree, as well as who referred the individual to genetic counselling. All identifiers were excluded from the data collection in order to protect the anonymity of the patients included in this study. The patient files were also analysed to determine whether genetic testing was performed, and, if it was, where it was performed

(locally or internationally), and what type of genetic testing was performed. The patient files were analysed to determine which genetic mutations, if any, were found in patients and whether cascade testing was performed on at-risk family members.

Risk Assessments

Two-hundred and three (n=203) patients were the first individuals in their family to attend genetic counselling for their personal and/or family history of cancer and were given a manual risk assessment by the genetic counsellor they saw at the time. These manual risk assessments were included in the letters that were sent to each patient summarising what was discussed in the genetic counselling session, a copy of which was included in each file. These manual risk assessments were assigned a risk profile on a scale from low risk to moderate risk to high risk as per the criteria already described. For this study, these manual risk assessments were converted to a number from 1 to 5: 1 – low risk for an inherited cancer syndrome , 2 – low to moderate risk, , 3 – moderate risk , 4 – moderate to high risk and 5 – high risk. This was done to be able to compare these manual risk assessments to the online computational risk assessment models' calculated risk.

Two subsets of files were analysed to compare the accuracy and utility of the risk assessment tools, CanRisk and PREMM$_5$, in a South African context. A total of 122 patients were selected based on the criteria below (**Figure 1**). CanRisk and PREMM$_5$ assessments were performed to determine the similarity of these to the manual risk assessments, and to determine the likelihood (percentage) of detecting a genetic mutation causative of HBOCS and Lynch syndrome, respectively. These risk assessment tools were chosen as they are often used by the genetic counsellors at the NHLS/WITS so as to aid the analysis of their cases.

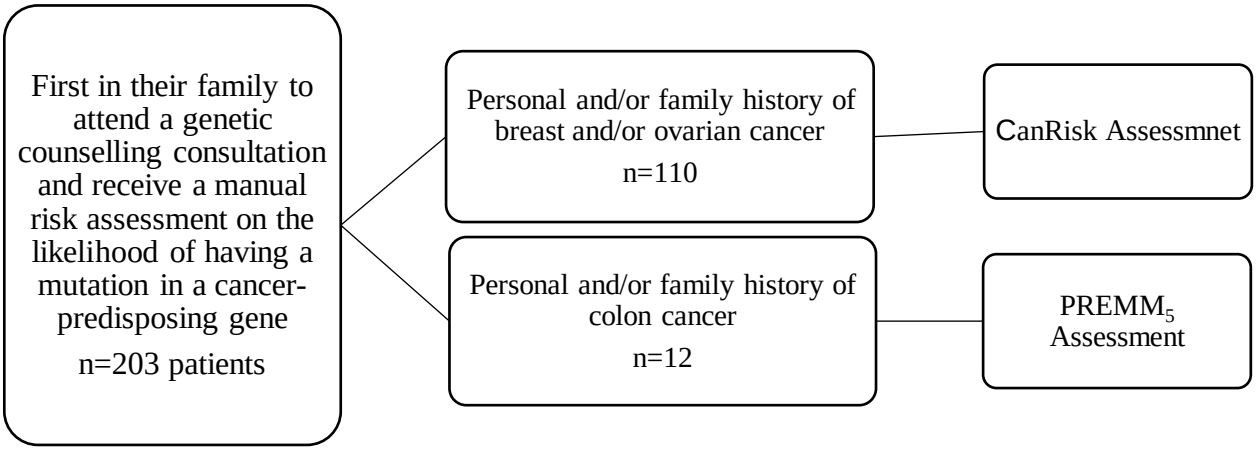


Fig. 1 The process that was used to select patients on which to perform CanRisk and PREMM5 risk assessments

The remainder of the population who were the first in their family to attend a genetic counselling session did not have a personal or family history of breast, ovarian or colon cancer (n=81). Those who already had a confirmed genetic mutation identified in their family were not included in these sub-cohorts. This is because they did not receive a manual risk assessment but rather received an empirical risk assessment that was as high as a 50% chance of having inherited the same mutation as their relative.

Statistical Analysis

Demographic and clinical characteristics were summarised using descriptive statistics. Categorical data were represented as percentages. Normality of continuous variables was assessed by determining the skewness and kurtosis of the collected data. Parametric data was presented as means ± standard deviations (SDs) and non-parametric data was presented as medians (Interquartile ranges (IQRs)). The Excel Statistical Analysis Application was used to determine whether any relationships and associations existed between the variables. A t-test was used to determine whether there was an association between opting for genetic testing and patient age (a continuous variable). Furthermore, to test for an association between the existence of a family history of cancer and the uptake of cascade testing (categorical variables), a Chi-Squared test was used. In the instances where *n* was less than 150, a Fisher's Exact test was used. For all statistical analyses, significance was assumed at a p value of <0.05.

A logistic regression analysis was performed to compare which risk assessment (manual or online risk assessment tool) was a more accurate predictor of finding a genetic mutation causative of HBOCS and Lynch syndrome.

Results

Study Population

A total of 315 patients were recorded to have attended a genetic counselling session for a personal and/or family history of cancer from January 2015 to December 2020. There were 18 files that were unaccounted for and seven files that had missing information and were excluded from this study.

A total of 290 (n=290) patients who attended a genetic counselling session for a personal and/or family history of cancer during the study period were included in the study. Most patients were seen in 2016 and 2017 (**Figure 2**) and there was an average of 48.3 patients seen each year over the six-year period.

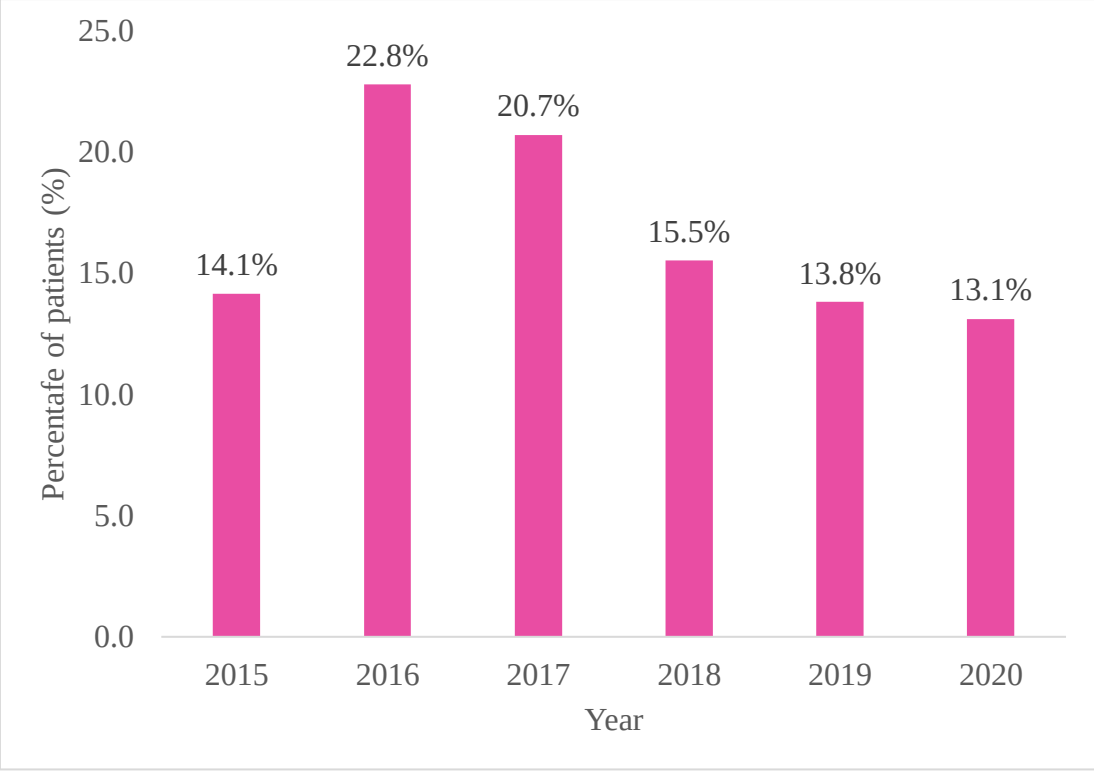


Fig. 2 The percentage of patients who were seen each year during the study period

The characteristics of the study population are provided in **.** The mean (SD) age of the patients was 47 ± 14.4 years and of the study population, 54.1% (157/290) were from a high-risk population group with Ashkenazi Jewish and/or Afrikaner ancestry. A total of 3.8% (11/290) of the patients had an isolated personal history of cancer, 50% (145/290) of the patients had only a family history of cancer, and 46.2% (134/290) had both a personal and family history of cancer. Of the patients who were diagnosed with cancer (with or without a family history of cancer), the mean (SD) age of their initial diagnosis was 45.0 ± 12.7 years.

Table 1: Characteristics of the patients

Characteristics	**N (%) or mean ± SD**
Age (years)	47 ± 14.4
Sex	
Male	48 (16.6%)
Female	242 (83.4%)
Race/Ethnicity	
Caucasian	247 (85.2%)
Black	16 (5.5%)
Indian	17 (5.9%)
South African Mixed Ancestry	6 (2.1%)
Asian	3 (1.0%)
Latino	1 (0.3%)
High Risk Population Ancestry	
Ashkenazi Jewish	63 (21.7%)
Afrikaner	89 (30.7%)
Both	5 (1.7%)
Not Specified	21 (7.2%)
None	112 (38.7%)
Personal History of Cancer only	11 (3.8%)
Personal and Family History of Cancer	134 (46.2%)
Mean age of Cancer diagnosis (years)	45.0 ± 12.7
Family History of Cancer only	145 (50.0%)

A total of 255/290 (87.9%) of patients belonged to a medical aid. A total of 70/290 (24.1%) of patients were referred to genetic counselling by an oncologist while 15.5% (45/290) and 10.0% (29/290) were referred by a surgeon and a family member, respectively. The rest of the referrals were from general practitioners, plastic surgeons, radiologists, gastroenterologists and gynaecologists.

Cancer Diagnoses

A total of 145/290 (50.0%) patients were diagnosed with cancer and 18.6% (27/145) of these patients were diagnosed with two or more cancers at the time of their consultation. Therefore, there were a total of 172 cancer diagnoses within the study population, the most prevalent cancer was breast cancer (**Fig. 3**).

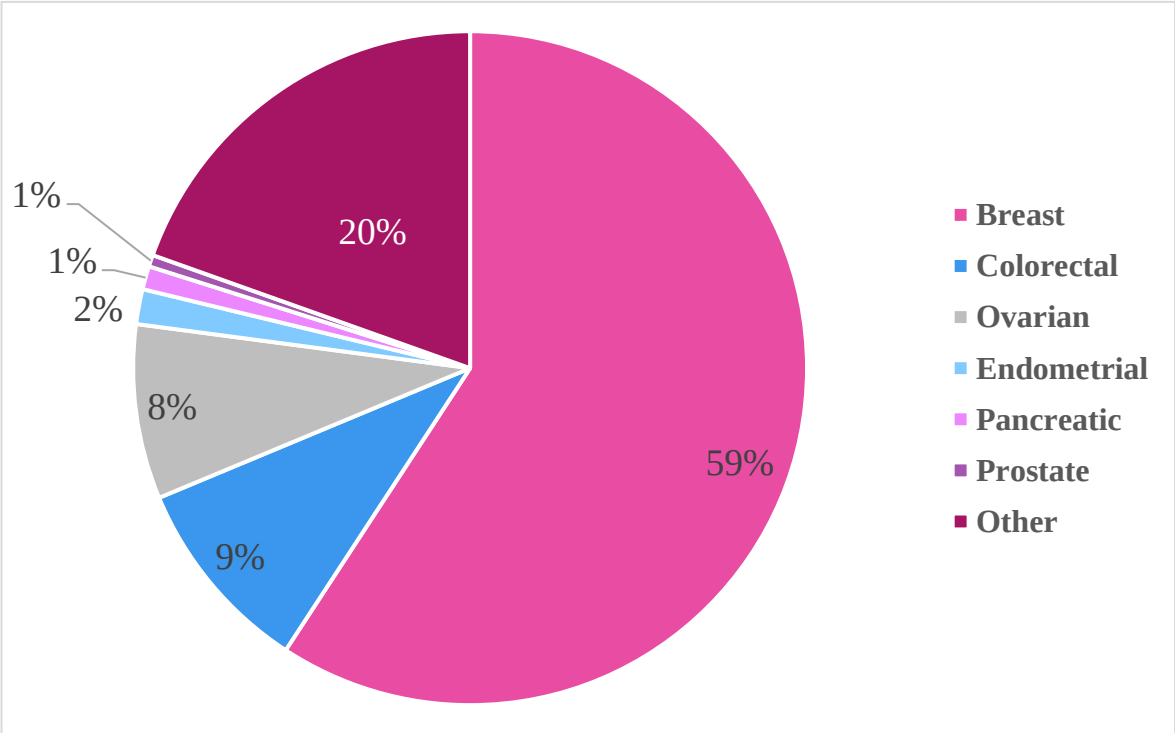


Fig. 3 The proportion of cancer diagnoses by type in the study population

The 'other' types of cancer making up 19.6% (35/179) of the total cancer diagnoses comprised cancers that are not strongly associated with inherited cancer syndromes such as bladder cancer, skin cancer, lung cancer, thyroid cancer, lymphoma and leukaemia.

Risk Assessment

It was observed that 30.0% (87/290) of the patients in the study population had a confirmed genetic mutation identified in their family and had come for genetic counselling to discuss predictive genetic testing. As they already had a genetic mutation identified in their family, they each had up to 50% risk of having inherited the same familial mutation.

In contrast, 70.0% (203/290) of the population were the first individuals in their family to attend genetic counselling for their personal and/or family history of cancer and received a manual risk assessment by the genetic counsellor who they saw at the time. It was observed that the mutation carrier probability for a genetic mutation determined by CanRisk was a statistically significant predictor of finding a genetic mutation causative of an inherited breast and ovarian cancer (p=0.01) in comparison to that of the manual risk assessments. PREMM$_5$ was a borderline predictor of finding a genetic mutation causative of Lynch syndrome (p=0.05) in comparison to that of the manual risk assessments.

Genetic Testing Uptake

The uptake of genetic testing was 71.0% (206/290) and patients were offered local and/or international testing that was available at the time of their consult (**Fig. 4**). A total of 129/206 (62.6%) pursued local genetic testing and 77/206 (37.4%) pursued genetic testing through international laboratories. There was an increased shift in the uptake of international testing versus local testing from 2019.

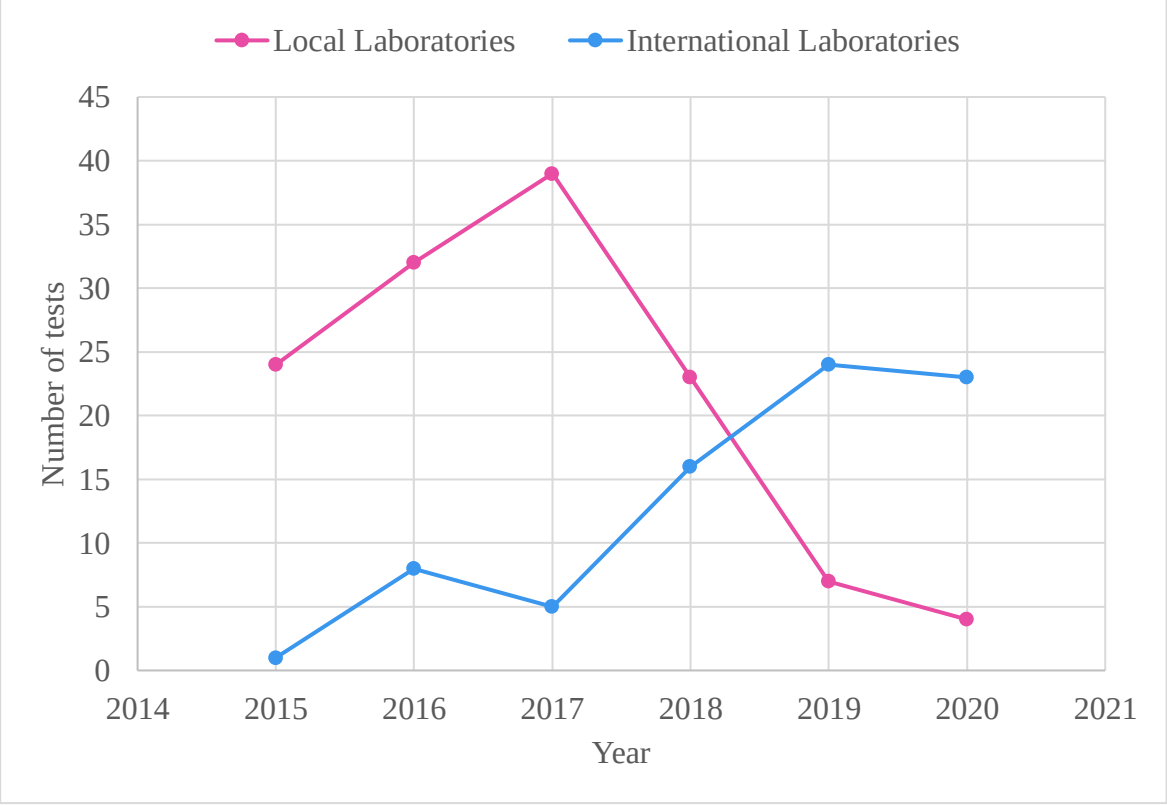


Fig. 4 The number of genetic tests performed between local and international laboratories from 2015 to 2020

The patients pursued single gene sequencing, *BRCA* founder mutation analysis, targeted genetic analysis or a multigene panel, depending on their personal and/or family history (**Fig. 5**). The majority (43.7%) of the patients pursued gene panel testing (90/206).

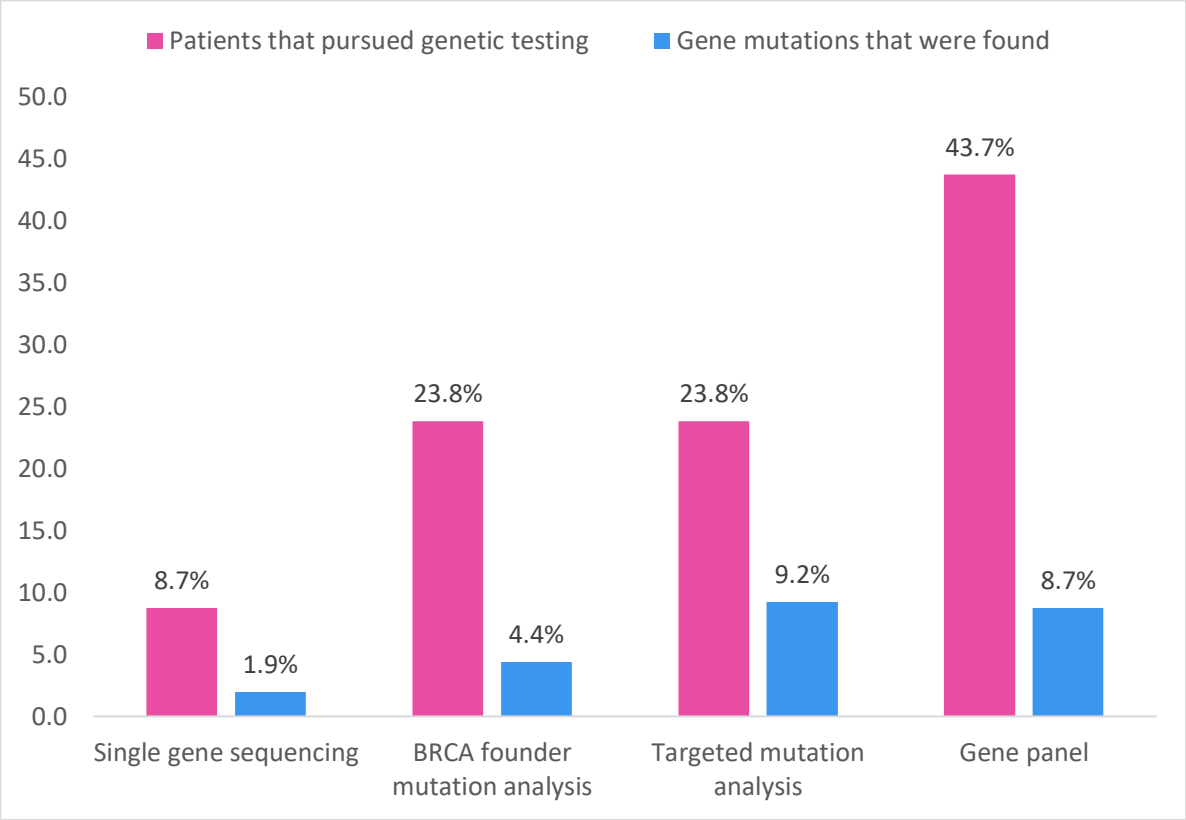


Fig. 5 The type of genetic testing that was utilized and the mutation pick-up rate

As seen in **Table 2**, there was no difference between the mean ages of those that pursued genetic testing and those that did not (p=0.079) and males and females were equally likely to pursue genetic testing (p=0.281). There was no association between having a personal history of cancer and the uptake of genetic testing; patients with and without a personal history were just as likely to pursue genetic testing (p=0.195). Similarly, it was found that there was no association between having a family history of cancer and the uptake of genetic testing; patients with and without a family history of cancer were just as likely to pursue genetic testing (p=0.085).

Table 2: The number of patients who accepted and declined genetic testing from 2015 to 2020

	Genetic Testing		p-value
	Accepted (n=206)	**Declined (n=84)**	
Mean Age (years)	47±6.9	44±6.7	0.079
Sex			0.281
Females	175	67	
Males	31	17	
Family history			0.085
Yes	201	78	
No	5	6	
Personal History			0.195
Yes	108	37	
No	98	47	

Genetic Test Results

A total of 50/206 (24.3%) of patients who pursued genetic testing were found to have a gene mutation. A total of 17/50 (34.0%) and 19/50 (38.0%) of the gene mutations were detected in the *BRCA1* and *BRCA2* genes, respectively (Table 3). A total of 20/36 (55.6%) of the genetic mutations identified in the *BRCA1* and *BRCA2* genes were Afrikaner and Ashkenazi Jewish founder mutations.

Table 3: The distribution of gene mutations that were found in patients who underwent genetic testing

Gene	Patients with mutations N (%)
BRCA1	17 (34.0%)
BRCA2	19 (38.0%)
ATM	2 (4.0%)
MLH1	2 (4.0%)
MSH2	2 (4.0%)
MSH6	2 (4.0%)
APC	1 (2.0%)
CHECK2	1 (2.0%)
MUTYH	1 (2.0%)
RAD51	1 (2.0%)
TERT	1 (2.0%)
TP53	1 (2.0%)
Total	50 (100.0%)

A total of 139/206 (67.5%) of the patients tested received a negative result. A variant of uncertain significance (VUS) was identified in 22/206 (10.7%) patients, five of whom had also received a positive result (5/50).

A total of 72.0% (36/50) of the genetic mutations detected in this study population were found in the *BRCA1* and *BRCA*2 genes. Of the patients who tested positive for a *BRCA* mutation, it was found that detecting a mutation in *BRCA1* is just as likely as finding a mutation in *BRCA*2 with regard to personal and family history of cancer (p=0.311), and sex of patient (p=0.683).

Cascade Testing

A total of 87/290 (30.0%) of the patient population had a confirmed genetic mutation in their family and had come for cascade genetic counselling and testing. A total of 69/87 (79.3%) of these individuals pursued cascade testing, of which 34.8% (24/69) received a positive result indicating that they had inherited the same familial mutation as their relative who had tested first. In contrast, 65.2% (45/69) received a negative result indicating that they had not inherited the same familial mutation as their relative.

It was also observed that the 50 patients, who received a positive result, had a cumulative number of 134 at-risk relatives, of whom 36.6% had arranged a genetic counselling consultation to clarify their risks. There were significantly more at-risk relatives who did not pursue genetic testing than those who did (p=0.001).

Discussion

The results of this study show that there has been a consistent number of patients who have attended genetic counselling for a suspected inherited cancer syndrome over a six-year period. The highest number of patients were seen in 2016 when the Clinical Section had the greatest number of staff compared to other years (personal communication, Shelley Macaulay). The lowest number of patients were seen in 2020 which is as expected as the COVID-19 pandemic caused a disruption of all healthcare services, including genetic counselling.

The majority of the study population comprised of patients with Afrikaner and Ashkenazi Jewish ancestry. This is expected as these population groups have a higher prevalence of

HBOCS; research has shown that one in forty women of Ashkenazi Jewish ancestry carry a *BRCA* mutation [23]. An increased awareness of this high prevalence may be behind the referrals to genetic services, especially in the private healthcare sector. The study population was also enriched with females which is consistent with other studies that state that women are more likely to be involved in refining their risks for having an inherited cancer syndrome than men [24]. This may be explained by the different social roles men and woman play in healthcare of the family [24]. Furthermore, males are less likely to seek out genetic services and are also less likely to communicate their genetic test results to their family, thereby barring cascade testing in a family [24]. Additionally, there may also be a misconception that mutations in the *BRCA1* and *BRCA2* genes only cause HBOCS in females [24]. Individuals with many different cancer types were referred to genetic counselling but the most frequent cancer in the study population was breast cancer at 59.2% (106/179). Given the fact that breast cancer predominantly affects females [24, 25] it is expected that females would make up the majority of the study population. Other studies, as well as the Globocan report, also describe breast cancer as the most common malignancy in South Africa [22, 25]. Additionally, *BRCA1* and *BRCA2* are the most prevalent genes associated with an inherited cancer syndrome [7].

This study showed that the CanRisk score was a better predictor of finding a mutation causative of inherited breast and ovarian cancer than the manual risk assessment given by genetic counsellors. This is consistent with another study by Seymour *et al* (2016) that found that the BOADICEA prediction model was a good indicator of high risk individuals [3]. CanRisk was designed and developed using a largely European Caucasian population. Our study population consisted of 85.2% Caucasian patients and so the utilisation of CanRisk can be extended to the South African Caucasian population. According to the results of this research, it is recommended that genetic counsellors in a similar setting to this study utilise online prediction models such as CanRisk and $PREMM_5$ rather than their manual risk assessments when counselling for an inherited cancer syndrome. However, CanRisk may not be as useful in other population groups and as such, more research is needed to determine which risk assessment tools are applicable to the understudied Black population in South Africa. There was a very small number of Black individuals in this study population (5.5%) which may be attributed to various reasons; the founder populations in South Africa are predominantly Caucasian [3], access to medical aid is skewed towards the Caucasian population [21] and the breast cancer risk is lower in Black patients [26].

The high uptake of genetic testing (71.0% (206/290)) seen in the study population may be attributed to various reasons. According to Hann *et al* (2017), individuals choose to pursue genetic testing to guide management of cancer risk, to reduce uncertainty and gain more information, especially for family members, to reduce anxiety regarding cancer risk, to plan for the future, and to create a sense of personal control [27]. The patients who pursued genetic testing in our study population are likely to have been more empowered and had taken the first step to come for genetic counselling.

Those who tested positive for a mutation causative of an inherited cancer syndrome (24.3%) were afforded the opportunity to pursue strategies and interventions that could significantly reduce cancer incidence and cancer related morbidity in themselves and their relatives [1]. Medical aids need to be made aware of the benefits of genetic testing which can lead to interventions that reduce cancer morbidity and avoiding prolonged and failed treatments which are often covered by medical aid schemes. Preventing cancer using genetic testing is a more cost-effective approach than treating cancer [28].

There was a high uptake (79.3%) of cascade testing in the sub-population who had sought genetic counselling due to a familial mutation. Patients who tested positive for the familial mutation could pursue tailored screening and management protocols [1, 8, 10]. Those who tested negative for the genetic mutation identified in their family (65.2% (45/69)), could have peace of mind and be reassured that they were not at increased risk of developing cancer. The family pedigrees of patients who tested positive for a mutation (not previously identified in a family) were assessed and it was noted that the uptake of cascade testing was not high for these at-risk relatives A total of 134 at-risk family members were identified by assessing family pedigrees and of these at-risk relatives, only 36.6% pursued cascade testing for the mutation identified in their family. This may be due to genetic testing being pursued through different genetic testing centres, or due to a time lag between when relatives learn that about the familial mutation and when they choose to pursue testing. This may explain the contradicting uptake of cascade testing between the two groups. However, studies by Samadder *et al* (2020) and Pollard *et al* (2019) showed that cascade testing is underutilised [1, 29]. They attributed the low uptake of cascade testing to the difficulty of sharing genetic test results with family members [1, 29]. They described the many factors that hinder disclosure of genetic test results such as, strained intra-familial relationships, family culture, geographic barriers, fear and anxiety experienced by the tested individual in having the burden to share their results and the fear experienced by their family members when confronted with the topic of cancer [1, 29]. It would be difficult for

us to determine whether the disparity in the uptake cascade testing between the two groups is due to a sampling error or because of the psychosocial implications associated with family communication.

Barriers to risk communication may explain why individuals decline testing. In our study, the uptake of genetic testing was not associated with patient sex, or personal and family history, suggesting that there may be more complex reasons as to why individuals accept and decline genetic testing. Individuals may choose not to pursue genetic testing due to fear and denial regarding possible results, lack of information, concern about the impact of genetic test results and how their family may respond, apprehension regarding confidentiality and the impact on medical and life insurance and cost [1, 12, 29]. Genetic counsellors have the potential to overcome some of these barriers by guiding individuals through the testing process, helping them navigate their genetic test results by providing them with information and psychosocial support as well as helping them disclose genetic test results to their family members [10].

It was observed that, over the six-year period of this study, the landscape of genetic testing offered in the South African private healthcare sector has changed and there has been a shift from local testing to predominantly international testing (**Figure 4**). International testing is more affordable, has a quicker turn-around time and offers a larger variety of multigene panels. In addition, international laboratories such as Invitae offer cascade genetic testing to family members at a discounted cost if a pathogenic or likely pathogenic mutation is found [22]. Despite these advantages, genetic testing at international laboratories is not covered by South African medical aid schemes. It is evident from this study that, more recently, genetic testing has moved away from local testing and is currently predominantly being performed internationally. and that patients are therefore independently liable for payment of the test. Medical aid schemes in South Africa need to take into account the benefits of international genetic testing in order to become more futuristic in their management of their clients. Medical aid schemes generally cover the costs of routine screening such as yearly mammograms and magnetic resonance imaging (MRI). However, genetic testing is a one-time cost that would provide information that would be valuable for the lifetime of a patient [28]. Genetic test results provide considerable benefits to individuals and their relatives who can pursue increased surveillance and risk-reducing strategies, such as prophylactic surgeries. Additionally, medical aid schemes would have to cover prolonged and failed treatments which could be avoided or directed by genetic testing [28]. For example, patients with a confirmed genetic mutation in their *BRCA1* or *BRCA2* genes are able to be treated with Poly-ADP ribose polymerase (PARP)

-inhibitors [30]. Poly-ADP ribose polymerase (PARP) is a specialised protein that prevents genetic mutations in cancer cells from accumulating, thereby extending their life cycle. PARP-inhibitors are a form of gene-therapy that prevents the progression of breast cancer and is considered to be precision medicine which is the way of the future [30].

It is important to note that the South African healthcare system is two-tiered, the private healthcare system and the state healthcare system. As previously mentioned, only 16% of the South African population has medical aid. Therefore, access to local and international genetic testing is limited. This means that the majority of the South African population do not have access to the same healthcare as those with a higher socioeconomic status. This is why it is important that quality healthcare is equally distributed within society so to ensure distributive justice.

If patients are aware of their genetic status, they have the opportunity to pursue effective management and screening in order to mitigate their cancer risk, or pursue tailored treatment strategies of a cancer diagnosis. This would ultimately reduce costs to medical aids and it would be beneficial for medical aids to cover and promote international gene testing. Additionally, if medical aid schemes were to cover the cost of international genetic testing, it would also increase the accessibility of multigene panel testing [28].

Limitations

This study looked at private patients who were mostly of Caucasian descent and almost half of whom had Afrikaner or Ashkenazi Jewish ancestry. Therefore, this study was enriched with high risk population groups who are at an increased risk of an inherited cancer syndrome, particularly HBOCS. Therefore, these results are not representative of the general South African population. In addition, as this was a retrospective file review, the data collected were dependent on the records that the genetic counsellor took at the time of the consultation. Lastly, this study only looked at a six -year period; family members may still come for predictive genetic counselling and cascade testing in the future.

Future Research Recommendations

As previously mentioned, a qualitative study would be beneficial to provide insight into why individuals accept and decline genetic testing. It may also be beneficial to do a qualitative study with representatives of medical aid schemes to determine their perceptions of genetic testing and whether they are aware of the competition that local laboratories are facing. Lastly, it would be valuable to perform a similar study at another genetic centre in South Africa, perhaps in the Western Cape, to determine whether the findings are consistent between the two centres.

Conclusion

Genetic counselling is essential in identifying individuals who may be at an increased risk of having an inherited cancer syndrome. Genetic test results have the ability to guide cancer management, surveillance and prevention, thereby reducing disease burden, not just in families, but in a population. Genetic testing to timeously determine one's genetic status, and the implementation of cancer screening and risk reducing measures, would be a more cost effective approach than the long term management and treatment of a cancer diagnosis. Genetic testing through international laboratories has become the preferred option in the past few years due to lower costs and faster turn-around times. Furthermore, some international laboratories offer free cascade testing within a certain period of time, to at-risk relatives once a mutation has been identified. Medical aid schemes in South Africa have an opportunity to realise the benefits of covering the costs of international genetic testing. In doing so, it is hoped that access to genetic testing in international laboratories may become more accessible within the healthcare system as a whole, including in the state health care sector. This should aid in addressing the inequality of access to healthcare in South Africa.

Declarations

Ethics Approval

Ethical Clearance was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (WITS) (Ethics clearance certificate: M210272) (*Appendix A*)

Funding and Competing Interests

The authors of this study did not receive any support from any organisation for the submitted work. The authors declare that they have no financial interests.

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Appendices

A. Ethics Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

02 March 2021

To Whom It May Concern

SUBJECT: **CONFIRMATION OF PROVISIONAL STUDY APPROVAL**
(This letter is not a clearance certificate - not yet cleared)
Protocol Ref No: M210272
Protocol Title: Genetic Testing for Inherited Cancers in Patients within the Private Healthcare Sector of South Africa
Principal Investigator: Miss Tasmyn Dale Scriven
Department: Pathology, Division of Human Genetics

This letter serves to confirm that the Human Research Ethic s Committee (Medical) has provisionally approved the above mentioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your district/institution.

The researcher has been informed that this letter is not a clearance certificate and that the study cannot commence without your approval and receipt of a clearance certificate from the HREC (Medical).

Should you have any queries, you may contact me at tel: 011 717 1234/2700/2656 or by email Rhulani.Mkansi@wits.ac.za or HREC-Medical.ResearchOffice@wits.ac.za

Yours Faithfully,

Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
02 MAR 2021
RESEARCH OFFICE HREC (Medical)
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C. Familial Cancer Submission Guidelines

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Instructions for Authors

Terminology

Please refer to the following article regarding terminology when reporting germline cancer susceptibility variants: Spurdle AB, Greville-Heygate S, Antoniou AC, et alTowards controlled terminology for reporting germline cancer susceptibility variants: an ENIGMA reportJournal of Medical Genetics 2019;56:347-357

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Manuscript Submission

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Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs.

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Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Scientific style

Please always use internationally accepted signs and symbols for units (SI units).

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

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- Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

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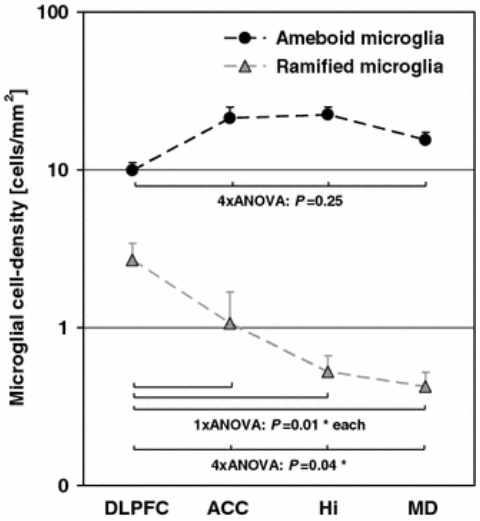
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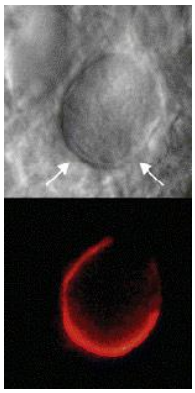
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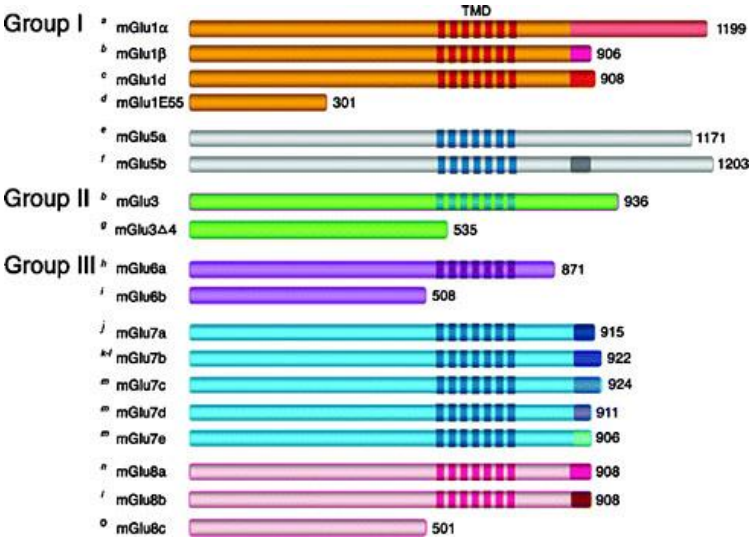
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Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: Filip1tm1a(KOMP)Wtsi RRID:MMRRC_055641-UCD
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Antibody: Luciferase antibody DSHB Cat# LUC-3, RRID:AB_2722109
Plasmid: mRuby3 plasmid RRID:Addgene_104005
Software: ImageJ Version 1.2.4 RRID:SCR_003070

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered’ should be included as the last line of the manuscript abstract.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal’s Instructions for Authors.

Checklists are available for a number of study designs, including:
Randomised trials (CONSORT) and Study protocols (SPIRIT)
Observational studies (STROBE)
Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)
Diagnostic/prognostic studies (STARD) and (TRIPOD)
Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).
- This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).
- Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.
- The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...)
- Examples of statements to be used for a retrospective study:
- Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.
- This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.
- This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

- This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.
- The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

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Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is

possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered "informed". However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found here. (Download docx, 36 kB)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for "Consent to participate":

Informed consent was obtained from all individual participants included in the study.
Informed consent was obtained from legal guardians.
Written informed consent was obtained from the parents.
Verbal informed consent was obtained prior to the interview.
Sample statements for "Consent to publish":
The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.
The participant has consented to the submission of the case report to the journal.
Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:
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Data availability statements

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