THE DEVELOPMENT OF A GENETIC COUNSELLING PROGRAM TO IDENTIFY, TEST AND MANAGE FAMILIES AT RISK FOR INHERITED COLORECTAL CANCER

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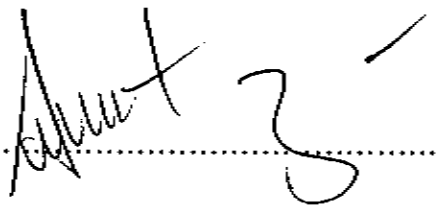
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Science in Medicine in Genetic Counselling

Johannesburg, 2008

DECLARATION

I, Andre van der Westhuizen, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in Genetic Counselling at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University



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24th day of October 2008

DEDICATION

I dedicate this work to my wife, Dr Debra Lynne Duff Hean, for her love, encouragement, continued support and kind motivation during my years of specialisation.

I also dedicate this work to my parents, Frank Johannes van der Westhuizen and Helen Margaret van der Westhuizen (Ellis) for their love, support and continued interest through all my university studies and my medical career.

PRESENTATIONS ARISING FROM THIS STUDY

Oral presentation:

- **van der Westhuizen A, Krause A (2007) The development of a screening program to identify individuals at risk for inherited colorectal cancer. Twelfth biennial congress of the South African Society of Human Genetics - at Golden Gate, Orange Free State, South Africa from 1-3 March 2007**

Poster presentation:

- **van der Westhuizen A, Krause A (2007) The development of a screening program to identify individuals at risk for inherited colorectal cancer in South Africa. Joint Meeting of the UK Cancer Genetics Group and Dutch Cancer Society with the 10th International Meeting on Psychosocial Aspects of Genetic Testing at Manchester Conference Centre, Manchester, United Kingdom from 22-24 May 2007**

ABSTRACT

The study was a pilot project aimed at identifying families at risk for inherited colorectal cancer. It was further integrated into developing a cancer genetics program for South Africa. No cancer genetics program is available in South Africa at present. A patient-based, self-administered questionnaire was used as a research tool to risk stratify families. Those families found to be at increased risk according to the questionnaire were subsequently counselled, tested and managed according to their risk. The value of a self-administered questionnaire in comparison with a genetic counselling interview in assessing the risk status of colorectal cancer patients was determined. The increase in cancer genetic referrals to the Division of Human Genetics at the University of the Witwatersrand and National Health Laboratory Service was assessed. The project was further aimed at establishing a multidisciplinary service for families at increased risk in collaboration with the specialists involved in their care. It was hoped that the need for cancer molecular genetic testing services would be highlighted and that awareness of the availability of cancer genetic services would be increased at the practices involved in the study. The final purpose of the research was the development of a comprehensive genetic counselling program for all the inherited cancers based on the principles learned in this pilot study.

The first step of the project was requesting staff and doctors at hospitals and clinics to distribute questionnaires to patients affected with colorectal cancer when they were treated or followed up for their cancer. Patients became research participants by agreeing to record their personal and family cancer histories on the self-administered questionnaire and signing

consent to allow access to their histopathology reports and medical files. The patients were asked to become research participants by the medical staff and/ or the doctors at the practices involved. All the patients who were recruited and completed the research tool became research participants and all the questionnaires (48) that were handed out to patients were completed. Research participants were recruited from two private practice oncology centres in Johannesburg and Pretoria, at Johannesburg Hospital's Oncology, Gastroenterology and Surgery Departments and at a private surgery practice in Johannesburg. The research tool questions were constructed by the writer. Some questions were based on clinical experience in the genetic counseling clinic and some were derived from the literature.

The second step of the program was to classify families into one of 3 risk categories (average, moderate or high risk) for inherited colorectal cancer based on the data obtained in the questionnaire.

The third and final step of the program was to arrange a follow-up consultation with a clinical geneticist for all the patients that were at moderate or high risk. Genetic counselling with a formal pedigree study and clinical examination was done during this consultation and patients/families were offered genetic testing and a management plan according to their risk. Patient's attitudes towards genetic counselling, further genetic testing and sharing of information with relatives were assessed during the consultation, but were not formally recorded. The final risk assessment after the consultation was compared to the initial risk category assigned in the questionnaire to test the reliability of the research tool.

Forty-eight (48) completed questionnaires were received; 33 families (69%) were at increased risk (moderate or high risk) and 15 families (31%) were at average risk. Twenty-nine (29) (60%) patients were seen and 28/29 (97%) were correctly classified from data obtained from

the questionnaire and remained in the increased risk category. A total of 7 families (25%) fulfilled the Amsterdam II clinical criteria for the diagnosis of hereditary non-polyposis colorectal cancer (HNPCC)/ Lynch syndrome and 18 families (64%) were at high risk for HNPCC. One patient (4%) had familial adenomatous polyposis (FAP) and 2 families (7%) were at moderate risk for colorectal cancer. All high risk patients were interested in genetic testing and wanted to bank DNA for future testing. The writer's impression after the genetic consultations was that most of the participants were positive about the service and that most of them confirmed that they would inform their relatives of their inherited risks.

The genetic counselling program developed through the use of a self-administered questionnaire was helpful in the identification of patients and families at increased risk for colorectal cancer. The research tool provided a reliable and acceptable way of collecting unverified, but extensive personal and family history of cancer. The program was also helpful in advising participants and their families about the multidisciplinary management of their inherited risks according to best practice. Consultations for inherited colorectal cancer increased by more than 80% to the Clinical Section of the Division of Human Genetics, University of the Witwatersrand. This study formed the basis from which a new and more comprehensive family cancer program was developed and introduced into the genetic counselling and testing service. The study also highlighted the urgent need for a molecular cancer genetic diagnostic service in Johannesburg.

ACKNOWLEDGEMENTS

I would like to thank the following individuals and organisations for their support in making this study possible:

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- Prof Amanda Krause- for her motivation and support for the project, for her enthusiasm in establishing cancer genetic services and for being my supervisor
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- Patients and their families- for participating in the research, for being positive about the establishment of cancer genetic services and for their prompt response in arranging to meet me for the genetic counselling appointments
- Prof Lizette van Rensburg- for her enthusiasm for cancer genetic research and for doing the cancer genetic testing on the patients recruited in this project
- Genetic Counsellors at the Division of Human Genetics- for helping to send out cascade letters to probands for their increased risk family members and for sending out consent forms for specialized testing of tumour tissue on high risk individuals
- National Health Laboratory Service for their support

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLES

LIST OF ABBREVIATIONS

AD- Autosomal dominant

AFAP-Attenuated familial adenomatous polyposis

APC- Adenomatous polyposis of colon

AR- Autosomal recessive

AXIN2- Axis inhibitor 2

BLM- Bloom syndrome gene

BMPR1A- Bone morphogenic protein receptor, type 1A

CI- Confidence interval

CRAC1- Colorectal adenomal and carcinoma-1

DCBE- Double contrast barium enema

DNA-Deoxyribonucleic acid

FAP- Familial adenomatous polyposis

HNPCC- Hereditary non-polyposis colorectal cancer

IHC- Immunohistochemistry

MADH4/SMADH4- Mothers against decapentaplegic, Drosophilia, homolog of, 4

MLH1- Mut L, E. coli, homolog of, 1

MMR-Mismatch repair genes

MSH- Microsatellite instability-High

MSH2- Mut S, E. coli, homolog of, 2

MSH6- Mut S, E. coli, homolog of, 6

MSI- Microsatellite instability

MYH- Mut Y, E. coli, homolog of

PMS2- Postmeiotic segregation increased, S. Cerevisiae, 2

PTEN- Phosphatase and Tensin homolog

STK11- Serine/Threonine protein kinase 11

1. INTRODUCTION

1.1 Preface

"In no other human morbid condition is the role of genetics as relevant as in cancer" (Genuardi, 2004). Tumour development is associated with quantitative, structural and/or functional changes of the genetic make-up of the cell. Cancer can therefore be viewed as a genomic disease of the somatic cell in that deranged genetic mechanisms are responsible for the process of neoplastic transformation. The gap has been bridged between the fields of somatic and Mendelian genetics by the discovery that some cancers can be attributed to the inheritance of germ line mutations that predispose individuals not only to rare, but also to common cancers. Knowledge of the genetic basis of inherited cancer has been accumulating rapidly over the past 15 years and has led to the development of a novel and fast evolving clinical practice (Genuardi, 2004).

There are a growing number of inherited cancer clinics worldwide. Most of these are multidisciplinary centres that deal with the multiple facets of the management of individuals affected with, or at risk for, inherited cancer. The management ranges from risk assessment, genetic counselling, genetic testing, addressing related ethical problems, to prevention and treatment. Genetic testing has become an increasingly informative tool in the diagnosis, prevention and treatment of disease. Progress in the prevention, molecular diagnosis and management of the inherited cancers has made clinical cancer genetics an essential component of the basic care of individuals and families at risk of an inherited cancer syndrome (Genuardi,

2004). It would be unwise for health care professionals not to give their patients the chance of benefiting from the new molecular developments in the field of cancer genetics. Society invests billions annually in developing new tests and drugs for cancer, but only a fraction is spent on modernising systems of care. Realigning priorities will not only be a smarter strategy, but will also save lives. This becomes a matter of ethics because of the principle of distributive justice; equal amounts of money should be spent on modernising systems of care.

A comprehensive inherited cancer program is urgently needed in South Africa. A detailed family history is of great importance for assessing risk in an inherited cancer program, but obtaining this is time consuming, labour intensive and expensive due to staff limitations and medical aid costs based on time spent with patients. It is infrequently accomplished in non-genetic clinical practice and this prevents appropriate referral of patients at increased risk for inherited cancer.

This study was a pilot project aimed at developing a genetic counselling program for inherited colorectal cancer. This was achieved through the use of a patient-based, self-administered questionnaire linked to an information sheet and consent form to risk stratify families and subsequently counsel, test and manage patients according to their risk. Secondary aims were to assess the reliability of the questionnaire, increase cancer genetic referrals to the Division of Human Genetics, University of the Witwatersrand and National Health Laboratory Service, create awareness of the availability of cancer genetic services and the need for molecular testing and to establish a multidisciplinary service for families at increased risk of inherited cancer. General observations regarding patients' and families' perceptions regarding the genetic counselling program were also made. The final outcome of the project was the

development of a comprehensive genetic counselling program for all the inherited cancers based on the principles learned. Incorrect or miss- diagnosis, inappropriate referrals and genetic testing without proper counselling will be prevented if this program is instituted at all levels of care.

1.2 Literature review

1.2.1 Inherited cancer

Cancer is a genetic disease that arises from the progressive accumulation of mutations. These mutations promote the selection of a clone of cells with deregulated growth (Tobias and Black, 2002). Cancer genes are currently classified into three broad classes; proto-oncogenes, tumour suppressor genes and DNA repair genes. Normal tissue homeostasis is maintained through the regulation of these three classes of genes. Mutations in the three classes of genes are mostly acquired in the cells of the specific organ where the cancer arises and are known as somatic mutations. Somatic mutations lead to sporadic cancer and 90-95% of cancers are sporadic. Occasionally, mutations are inherited through the germline and these then predispose the individual to cancer development. Cancer is a multi-step process which invariably involves the accumulation of both inherited mutations and somatic mutations before cancer develops.

The germ-line mutations in tumour- suppressor and DNA mismatch repair genes are inherited in an autosomal dominant way and follow basic Mendelian principles with a 50% chance of being passed on to the next generation. The penetrance however varies because a second somatic mutation in the same gene on the other chromosome needs to occur before cancer development is initiated. Thus, two mutated copies need to be present before function is lost

and they therefore behave as recessive genes at the cellular level. In proto-oncogenes one mutation is enough to activate the cells to grow.

Most inherited cancers and all the inherited colorectal cancer syndromes are due to inherited mutations in tumour suppressor or mismatch repair genes. The flow diagram shown in **Figure 1.1** demonstrates why inherited cancers occur at a younger age than the average for the particular cancer and why they are often seen in multiple family members and in successive generations (the first mutation is dominantly inherited). In sporadic cancer both the mutations are acquired in the lifetime of the individual.

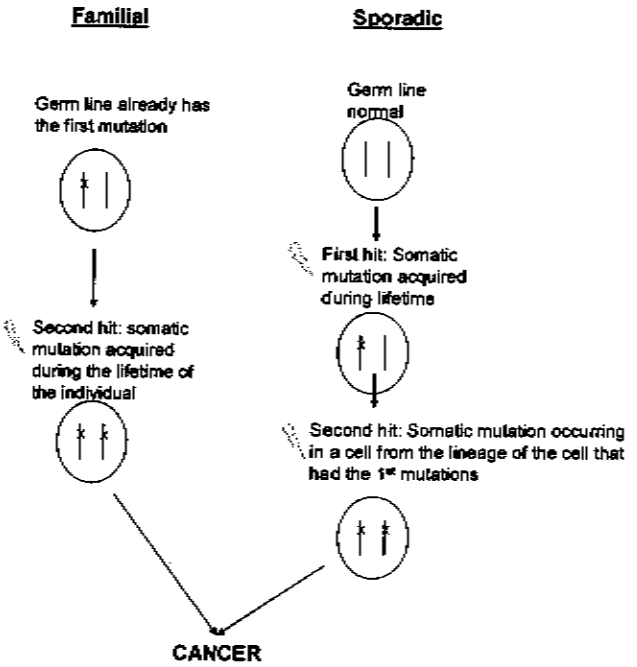


Figure 1.1 Difference between familial and sporadic cancer

Genetic susceptibility accounts for 5-10% of colorectal cancer, but germline mutations in the known single genes only account for 1-2% of cases (reviewed in Firth, Hurst, Hall, 2005). A combination of more common multiple lower-penetrance genes accounts for the shortfall seen and most of these genes still need to be elucidated. A family history of the disease significantly increases the risk to relatives and the challenge is to classify families into risk categories. This is important to identify those families that are likely to carry a germline mutation in a defined gene that will confer a high lifetime risk for colorectal cancer and to distinguish these families from families who have a reasonably strong genetic risk, but do not carry a mutation. These families are then known to be at moderate risk and targeted surveillance guidelines need to be implemented in this group as well (reviewed in Firth, et al. 2005). The main approach to achieve this is to get as much information as possible by integration of information from the family tree, the histopathology reports, cancer registries and sometimes suggestive syndromic features on clinical examination.

1.2.2 Magnitude of the problem

The field of clinical cancer genetics dealing specifically with inherited cancers has now grown exponentially and has become a recognized subspeciality of clinical genetics in Europe, Australia, Canada and the United States of America (Kausmeyer, Lengerich, Kluhsman, et al. 2006). There are more than 450 genetic counselling professionals in the United States who specialize in cancer genetics in the more than 300 cancer genetic programs (Kausmeyer, et al. 2006).

A survey conducted in seven European countries in 2003 showed that the number of cancer genetic centres ranged from 8 (in Belgium) to 37 (in France). The average population served by each centre ranged from 0.59 million (in Israel) to 3.32 million (in Italy) and the annual number of patients seen in each of the centres ranged from 200 to over 1700. Each of the centres has a multidisciplinary team involved in the management of the patients and all the patients have access to psychological support. All the centres had access to a laboratory offering DNA testing for breast and colorectal cancer predisposing genes and many other inherited cancers depending on the needs of the specific population. Collection of pedigree data, risk assessment strategies/ programs and genetic testing protocols were comparable in all the centres (Hopwood, van Asperen , Borreani, et al. 2003).

The population of Gauteng, South Africa, served by our Clinical Section of the Division of Human Genetics, is larger (approximately 8 million people) than the population served by the largest centre in the European survey. In the West Midlands in the United Kingdom, inherited cancer referrals constituted <1% (<20 cases) of all clinical genetic referrals in 1991, whereas they represented over 30% of cases (>1000) in 1998-1999 (reviewed in Cole, Sleightholme, 2000).

There is currently a low level of referrals for cancer genetics consultation to our genetic counselling clinics in Johannesburg. This is primarily because there is no effective strategy in place at primary, secondary or tertiary level to identify individuals at high risk for inherited cancer. We currently see only a very small fraction of the patients and families that need a clinical genetic consultation for inherited cancer. Referrals to our clinics for cancer genetics comprised less than 10% of the total number of referrals for the past 5 years and from 2001 to

2005 only 3 patients were referred for inherited colorectal cancer (patient statistical data from the Division of Human Genetics, University of the Witwatersrand and National Health Laboratory Service).

The above statistics show that there is a definite need to expand clinical cancer genetic referrals, clinical cancer genetic and counselling services and to institute a laboratory diagnostic service for the inherited cancer syndromes in our population.

Due to the magnitude of the problem and the fact that there are over 60 inherited cancer syndromes with over 80 of the genes for these syndromes already cloned (Genuardi, 2004), a decision was made that this study would aim to set up a risk assessment strategy for inherited colorectal cancer only through the use of a patient-based questionnaire. This research project served as a pilot study for the subsequent development of a large scale inherited cancer program at all the levels of care (primary, secondary and tertiary) that would be extended to all inherited cancers. The principles arising from this project would be used in developing this comprehensive program.

1.2.3 Inherited cancer risk assessment

The variability of the risk assessment criteria used among institutions and individual clinicians has been a major limitation of cancer family risk assessment. Accurate reporting of the family history helps to risk stratify patients and this in turn determines surveillance and prevention interventions (Murff, Spigel, Syngal, 2004).

"The most important step leading to the diagnosis of a hereditary cancer syndrome is the compilation of a thorough family history of cancer" (Lynch, de la Chapelle, 2003). Algorithms that predict individuals who may be candidates for genetic testing rely almost exclusively on information obtained from the family history. A false negative family cancer history will result in an underestimation of cancer risk and this will lead to missed opportunities for cancer surveillance and detection (Murff et al. 2004).

Failure to collect accurate histories and the subsequent inadequate management of the patient's and family's cancer risk will result in substandard care. There have been several cases in the literature that have resulted in malpractice litigation (Severin, 1996). Conversely, severe stress can be caused if the patient has a false belief in a positive family cancer history. Overestimation of risk may also lead to unnecessary procedures, treatment and cancer surveillance which will lead to escalating costs as well as emotional trauma.

A detailed family history with at least three generations is of great importance for assessing the risk of inherited cancer, but obtaining this is time consuming, labour intensive and infrequently accomplished in general clinical practice. Confirmation of family history information is important before accurate risk stratification can be done. Many physicians lack adequate training in genetics to identify and refer appropriate candidates for cancer genetic counselling (Hunter, Wright, Cappelli, et al. 1998). Clear guidelines need to be followed to ensure that all individuals and/or families at risk are identified and referred appropriately. The current reality of direct-to-consumer advertising of genetic testing on the Internet also increases confusion and anxiety levels in the general public and can lead to inappropriate self-referrals.

Family history data collection tools are used in many countries to overcome the problem of inadequate family cancer history information. This may take the form of a computer based data collection tool or a printed questionnaire. A family cancer history questionnaire on first degree relatives was validated in two European centres through the Clinical Cancer Research Unit in Basel, Switzerland. The sensitivity of the questionnaire was 85% (Trieste) and 74% (Basel) respectively; the specificity was 97% in both centers and the overall accuracy 95% (Trieste) and 94% (Basel) (Mussio, Weber, Brunetti, et al. 1998).

The information provided on first degree relatives is however not adequate for risk calculation, as cancer histories in second degree relatives are also important to make a final risk assessment. In a study that evaluated the test-retest reliability of family cancer histories performed with a computerized tool in first and second degree relatives it was found that the histories in second degree relatives were only slightly poorer than in first degree relatives (φ =0.94 for cancers in first-degree and φ=0.91 in second degree relatives) (Acheson, Zyzanski, Stange, et al. 2006).

An evidence-based analysis on the accuracy of a family cancer history in overseas cancer centres has also found that patient reported histories are accurate and valuable for colon and breast cancer risk assessments for first-degree relatives (Murff et al. 2004). There are currently no data available on this topic in the South African medical literature. When family histories of colon cancer were checked in a research study in Utah (Kerber, Slattery, 1997) a sensitivity of 73% (95% CI, 54%-86%) was obtained. In this study, the investigators compared self-reported family history of colon cancer to a computerized Utah Population Database, which

was created by linking genealogical records with the state cancer registry. The kappa score, a measure of overall agreement between the reported family history and the database, was 0.56 (95% CI, 0.45-0.66), indicating moderately good agreement. This study found that higher sensitivities were observed among younger subjects, females reported family cancer history slightly better than males and that a college education was not consistently associated with a more accurate reporting of family cancer history. What patients tell clinicians about their family histories is therefore a reasonably good indicator of actual history.

Some cancer genetic clinics in the United States, Europe, Canada and Australia use a computerized tool to collect family history information (Acheson, et al. 2006). A self-administered, computerized tool for collecting a family history of cancer was validated and the test-retest reliability was found to be high (Acheson, et al. 2006).

At the congress of genetic counsellors in the United States of America in October 2006, a study was presented that evaluated the accuracy of self-administered family cancer history questionnaires as a genetic counselling tool in the familial cancer setting at a familial breast and ovarian clinic in Toronto, Canada (McCuaig, Armel, Finch, et al. 2007). In this study it was found that 59% of cancer clinics in the province of Ontario use a family history questionnaire to create a patient's family pedigree. They updated the family history questionnaires by asking targeted questions during a genetic counselling session and found that in only 15% of families (121 participants) the history required changes that led to a new risk assessment and that in 5% of families changes altered the family's eligibility for genetic testing. Change in genetic testing eligibility was almost always accompanied by a change in risk assessment (5/6 families). They did not find a statistically significant change in genetic

testing eligibility prior to and after genetic counselling, but found a statistically significant change in risk assessment prior to and post genetic counselling. This level of change in risk assessment was deemed acceptable to continue the use of the family history questionnaire in their setting. Updating the questionnaire during a genetic counselling session therefore allowed for completion of the information obtained by the family history questionnaire and did not significantly alter genetic testing eligibility. It was also found that information that was most commonly added during counselling was a change in cancer diagnosis, particularly in distant family members (4^{th} degree relatives or grandparent's siblings). This study concluded that the family history questionnaire is an effective tool and that it can also save approximately 20-30 minute per counselling session. The investigators have developed a new version of their previous family history questionnaire based on the variables that were predictors of a change of risk assessment (ethnic background and consanguinity) and made it more user-friendly and are currently exploring if the new version of the family history questionnaire has improved accuracy (McCuaig, et al. 2007).

1.2.4 Creating cancer genetic service awareness

Clinicians and other health care workers in South Africa are not yet fully aware of the importance of genetic counselling in the management of patients and families with an inherited cancer syndrome. Once it is clear that a patient has a familial form of cancer, it is mandatory to offer the patient and his/her family genetic counselling. It must provide the patient and the extended family with important details about the genetic risk of cancer at specific sites (on the basis of the natural history of the specific cancer syndrome), the management options, surveillance and preventative strategies and the cost and availability of genetic testing (Lynch and de la Chapelle, 2003).

Genetic counselling should always be a face-to-face interview and should be given to individual family members separately as their needs may differ. Counselling should also take place in a quiet environment away from the stresses of a busy clinic, especially where patients are given chemotherapy in an oncology practice (Kausmeyer, et al, 2006). Informed consent for genetic testing and access to histopathology data forms an essential part of the process. This implies that the patient has received genetic counselling and adequate information about the syndrome, the genetic tests available and the importance of histopathology data. A document should be signed to that effect (Lynch and de la Chapelle, 2003).

There is also an obligation to inform the affected member of the family to notify his or her high risk relatives of their inherited risks once a diagnosis of a hereditary cancer syndrome is considered. Testing of one individual in a family may imply an increased risk to his/her relatives. There is an ethical obligation to warn ("duty to warn") a patient's family members

about hereditary disease risks (Offit, Groeger, Turner, et al. 2004). This may also then create conflict between the physician's obligations to respect the privacy of genetic information vs. the potential liabilities resulting from the physician's failure to notify relatives at risk (Offit, et al. 2004). There have already been three lawsuits in the United States of America because of failure to warn family members about hereditary disease risks. The health professional has a responsibility to encourage but not coerce the sharing of genetic information in families. The boundaries imposed by the ethical practice of medicine should be respected, as well as the boundaries imposed by the law (Offit, et al. 2004). Predictive genetic counselling and genetic testing (if available) should therefore subsequently be performed in consenting relatives (Lynch and de la Chapelle, 2003). It is clear from the above that cancer genetic services should be seen as a separate and essential part of the holistic management of patients as part of a multidisciplinary cancer team.

The role of the clinical geneticist and the genetic counsellor is paramount in the inherited cancer program and in the ultimate identification of patients and families requiring a genetic work-up. Experience in the field of medical genetics and genetic counselling is essential in dealing with the many implications of a familial cancer syndrome. There is currently a need for the correct management and care of high and moderate risk patients. In inherited colorectal cancer, this team needs to include a medical geneticist, genetic counsellors, a surgeon or a physician/ gastroenterologist and an oncologist. A multidisciplinary service will correctly assess, manage and screen individuals and families that are at high or moderate risk for an inherited colorectal cancer syndrome. Comprehensive management and care can only effectively be done in the context of a multidisciplinary team.

The clinical geneticist must perform a clinical examination and interpret histopathology reports of individuals and families to identify an inherited cancer syndrome. Many of the inherited colorectal cancer syndromes have variable clinical features and differentiation on a clinical level can be challenging. Many of the rarer inherited syndromes can only be identified clinically. The role of the medical geneticist is also to address ethical and other sensitive issues including discrimination and confidentiality often seen to be related to genetic testing and genetic risk.

The psychosocial implications of an inherited cancer syndrome diagnosis in a family are also profound and genetic counselling needs to be in place to address these issues. Time should be spent with individuals and/or families to support, inform and educate them regarding their diagnosis, risks and the risks to other family members. This may then also lead to cascade testing and counselling of many family members at risk of inheriting the cancer syndrome. The implications for future generations should also be addressed in the counselling session.

Awareness should also be created that genetic testing cannot be offered to just anyone, especially with the current threat of privatization of genetic testing in South Africa and direct-to- consumer access of information and testing via the Internet. Direct genetic testing is not cost-effective due to over servicing and is dangerous due to ethical issues related to discrimination as well as uncertainties surrounding the quality of the genetic testing. The limitations of genetic testing are also not discussed, patients do not understand the implications of positive and negative results and patients and families do not get psychological support or follow-up.

Many individuals may also decide after counselling that they do not want genetic testing to be done for various personal reasons and health care professionals are not always aware of this. Fear of discrimination and concerns about psychological and psychosocial issues may present barriers to the current strategies to prevent cancer (Hadley, Jenkins, Dimond, et al 2003). This emphasizes the need for an inherited cancer program at all levels of care to identify those individuals and families who are truly at increased risk and who need genetic counselling and testing.

1.2.5 Inherited colorectal cancer

1.2.5.1 Burden of disease

For colorectal cancer, a yearly incidence of about 50 new cases for every 100,000 persons is estimated in the USA, Australasia and Europe. The individual lifetime risk for colorectal cancer approaches 5% in these countries (Baglioni and Genuardi, 2004). Colon cancer is the second leading cause of death from cancer in the United States and presents a major burden in the western world. It is one of the five leading cancers in South Africa according to the South African Cancer Registry (Mqoqi, Kellet, Sitas, et al. 2004). The population prevalence of a family history of colon cancer is high in the western world and has been estimated to be between 2% and 9. 4% (Johnson, Lancaster, Fuller, et al. 1995) (Scheuner, Wang, Raffel, et al.1997). Patients who have a familial risk (those who have two or more first- or second degree relatives, or both with colorectal cancer) constitute approximately 20 percent of all colorectal cancer patients (Lynch and de la Chapelle, 2003). Approximately 5-10% of the total burden of colorectal cancer is inherited in a Mendelian fashion (Lynch and de la Chapelle,

2003). The lifetime risk of colorectal cancer in those with two first degree relatives affected is 1 in 6. This is high if compared to the population risk of 1 in 50 (in the western population). If the family pedigree is clearly autosomal dominant, this risk increases to as high as 1 in 2 (Goel, 2001).

1.2.5.2 Colorectal cancer in South Africa

The above figures (section 1.2.5.1) suggest that there may be a large group of patients with inherited colorectal cancer who are not referred and not managed appropriately in the greater Johannesburg area. Population data for colorectal cancer in South Africa were available for 1999 at the time of writing up this research report (Mqoqi, Kellet, Sitas, et al 2004) **(Table 1.1)**. These data are limited pathological data and are based only on histologically confirmed colorectal cancer cases seen post surgery at private pathology laboratories and the histopathology laboratories of the National Health Laboratory Service in South Africa.

Table 1.1- Population data for colorectal cancer in South Africa

Population	Male	Female
White	25.4/100 000	17.5/100 000
Asian	14.3/100 000	7.3/100 000
Mixed Ancestry/ Coloured	14.1/100 000	9.7/100 000
Black	3.0/100 000	2.3/100 000

A total of 1 245 colorectal cancers were reported in South Africa in 1999 and the figure is approximately similar to figures reported in previous years (Mqoqi, et al. 2004). An estimated 62-124 (5-10%) of these may have been inherited in a Mendelian fashion and if the past 5 years are taken into account, 300-600 inherited colorectal cancer patients in South Africa may not have been ascertained, not offered further pathological and genetic testing and not appropriately managed or counselled. These numbers do not reveal the many family members of these affected individuals that may also be at risk. At risk family members should also be offered genetic counselling in a cascade fashion and genetic testing where appropriate. All family members at risk should also be managed with surveillance and preventative measures according to their individual risk. The further counselling, care and follow-up of patients and families with an inherited colorectal cancer syndrome are essential components of long term management.

1.2.5.3 Genetic basis of inherited colorectal cancer

The genes for many of the colorectal cancer syndromes and for conditions associated with an increased colorectal cancer risk that are inherited in a Mendelian fashion have been cloned (Baglioni and Genuardi, 2004). Many of them are well-characterised autosomal dominantly inherited syndromes (Baglioni and Genuardi, 2004) (**Table 1. 2**).

Table 1. 2 Inherited colorectal cancer syndromes with known genes

Syndrome	Gene	Inheritance
Familial adenomatous polyposis (FAP)	*APC* (5q21-q22)	Autosomal Dominant (AD)
FAP	*MYH* (1p34.3)	Autosomal recessive (AR)
Gardner syndrome	*APC* (5q21-q22)	AD
Lynch syndrome (HNPCC)	*MLH1* (3p21.3), *MSH2* (2p22-p21), *MSH6* (2p16), *PMS2* (7p22)	AD
Peutz-Jeghers syndrome	*STK11* (19p13.3)	AD
Juvenile polyposis	*BMPR1A* (10q22.3), *MADH4/SMADH4* (18q21.1)	AD
Bloom syndrome	*BLM* (15q26.1)	AR
Hereditary mixed polyposis	*CRAC1* (15q15.3)	AD
Cowden syndrome	*PTEN* (10q23.31)	AD
Banayan- Riley- Rivulcaba (BRR syndrome)	*PTEN* (10q23.31)	AD
Familial permanent tooth agenesis and colon cancer	*AXIN2* (17q24)	AD

The most common of these syndromes are Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) and these two syndromes will be discussed in more detail.

1.2.5.3.1 Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC)

Five cardinal features exist that will help to identify families affected with hereditary non polyposis colorectal cancer (HNPCC) (Lynch and de la Chapelle, 2003). These include- earlier average age of onset of colorectal cancer (45 years average), a particular pattern of primary cancers segregates within a pedigree (cancer of the colon, endometrium, small bowel, ureter or renal pelvis), the survival differs from the norm for the specific cancer (prolonged), there are distinguishing histopathological features present (right sided with signet cell histology or undifferentiated pattern) and a germ line genetic mutation is present in the affected family members. HNPCC is due to autosomal dominant inheritance of a mutation in one of the genes involved in the DNA mismatch repair system; know as the mismatch repair (MMR) genes. The MMR genes that account for most (>90%) of the cases are *MSH2* (2p21) and *MLH1* (3p22.3) and they are equally distributed (reviewed in Firth, et al. 2005). A very small number of families (< 5%) have mutations in *MSH6* (2p22.3), while < 1% of families have mutations in *PMS2* (7p22.1) (Firth, et al. 2005). All classes of mutation are associated with HNPCC and include nonsense, frameshift, splice site, missense, rearrangements and whole exon deletions/duplications. HNPCC only accounts for approximately 1% of colorectal cancers and its prevalence is of the order of 1:3000 (reviewed in Firth, et al. 2005). In some populations a founder effect is seen, for example in the Finns (reviewed in Firth, et al. 2005).

1.2.5.3.1.1 Clinical diagnosis of Lynch syndrome/HNPCC

The Amsterdam criteria (**Table 1.3**) are used to make a provisional clinical diagnosis of HNPCC (Vasen, Mecklin, Meera Khan, et al. 1991). These criteria are not inclusive enough to

decide who needs genetic counselling or genetic testing, but are helpful in deciding clinically who is most likely to have a positive genetic test in the high risk patient group. The initial criteria have now been revised to include all the HNPCC- associated extracolonic cancers and are known as the Amsterdam II criteria (**Table 1.4**) (Vasen, et al. 1991).

Table 1.3 Amsterdam I criteria

There should be at least **three** relatives with colorectal cancer **and**

1) One should be a first degree relative of the other two
2) At least two successive generations should be affected
3) At least one individual should be diagnosed before the age of 50 years
4) Familial adenomatous polyposis (FAP) should be excluded
5) Tumours should be verified by pathological examination

Table 1.4 Revised Amsterdam criteria/Amsterdam II criteria

There should be at least **three** relatives with colorectal cancer and/or a HNPCC associated cancer (cancer of endometrium, small bowel, ureter or renal pelvis) **and**

1) One should be a first degree relative of the other two
2) At least two successive generations should be affected
3) At least one individual should be diagnosed before the age of 50 years
4) Familial adenomatous polyposis (FAP) should be excluded
5) Tumours should be verified by pathological examination.

1.2.5.3.1.2 Criteria for genetic testing of Lynch syndrome/HNPCC

As mentioned, there are further criteria, known as the Bethesda criteria (**Table 1.5**) (Rodriques-Bigas, Bolan, Hamilton, et al. 1997) which were used in the identification of individuals in the high risk category in the patients at risk for HNPCC who needed to be considered for specialised tumour genetic testing and pathological testing. This includes microsatellite instability (MSI) testing and immunohistochemical staining (IHC). Loss of the mismatch repair gene proteins (MMR) in a tumour manifests as microsatellite instability and it is defined as the presence of extra alleles at a microsatellite when compared to normal DNA of the same individual (reviewed in Firth, et al. 2005). The MSI is due to insertion/deletion mutations at repeats and is best observed at di- and mononucleotide repeats. Up to 20% of acquired/sporadic cancers show MSI and it has a poor positive predictive value for HNPCC. Lack of MSI however confers a high negative predictive value and it is therefore an excellent initial screening test for HNPCC (reviewed in Firth, et al. 2005). IHC testing makes it possible to test tumours for the loss or abnormality of MMR protein expression in tumour tissue. Loss of expression is almost always associated with MSI (reviewed in Firth, et al. 2005) and it helps in directing genetic testing by targeting germ-line testing only to the samples from which the proteins are lost on IHC staining. IHC is not as sensitive as MSI and MSI is still indicated to exclude HNPCC if a tumour shows normal IHC (reviewed in Firth, et al. 2005).

Testing of tumour tissue is therefore the first step before germ-line genetic testing should be undertaken in high risk families that do not fulfill the Amsterdam criteria, as MSI is a sensitive screening test. Subsequent IHC can direct germ line genetic testing and is more cost-effective and it makes sequencing of all the mismatch repair genes involved in HNPCC unnecessary.

Germ line genetic testing is directed by the results of these specialized pathological tests. The flow- diagram (**Figure 1.2**) illustrated in the following section (**1.2.5.3.1.3**) demonstrates the approach and genetic testing of Amsterdam criteria positive patients/families (**Table 1.4**) and Bethesda criteria positive high risk patients/families (**Table 1.5**).

Table 1.5 Revised Bethesda criteria

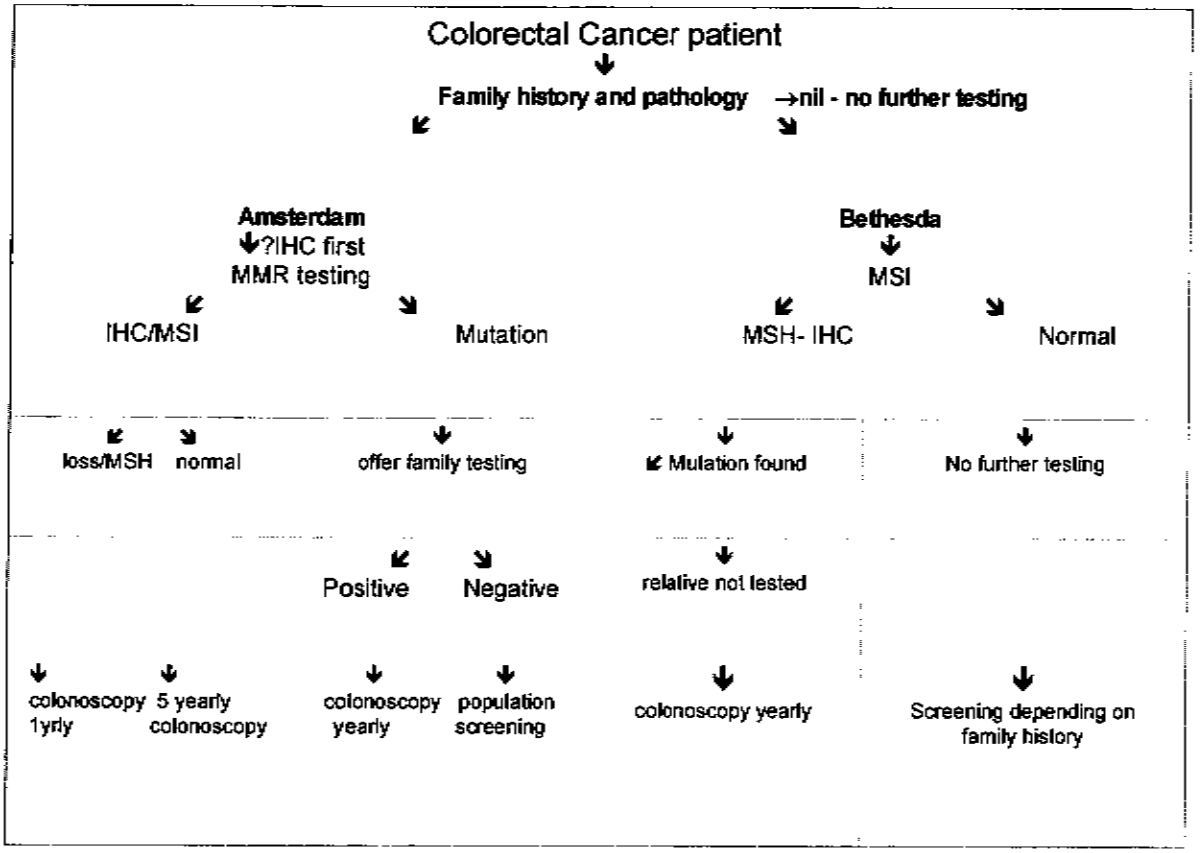
1)	Amsterdam *II* criteria positive	OR
2)	Individuals with two HNPCC cancers (including synchronous/ metachronous colorectal cancers)	OR
3)	Individuals with colorectal cancer and a first degree relative with colorectal cancer and/or an HNPCC extracolonic cancer and/or colorectal adenoma (cancer< 50 years and adenoma < 40 years).	OR
4)	Colorectal or endometrial cancer < 50 years	OR
5)	Right sided colorectal cancer with undifferentiated pattern on histology < 50 years	OR
6)	Signet cell type colorectal carcinoma < 50 years	OR
7)	Colorectal adenoma < 40 years	OR
8)	Absence of mismatch repair proteins on immunohistochemistry	

The Bethesda criteria have been modified by the American Gastroenterology Association (Association AG. American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing, 2001). They were recently revised again to include immunohistochemistry (absence of mismatch repair gene proteins on histopathological staining with antibodies directed against these proteiens) as an inclusion criterion (criterion **8** in **Table 1.5**) for microsatellite instability testing (Umar, Boland, Terdiman, et al. 2004)

(Banerjea, Clark, Dorudi, 2005). Immunohistochemistry is not routinely done on colorectal cancer histopathology samples in South Africa at present and therefore this recently revised guideline could not be used in this research report to select patients who needed to have DNA banking.

1.2.5.3.1.3 Genetic work-up and management of Lynch syndrome/HNPCC

The genetic work-up and management of Lynch syndrome (HNPCC) is a step-wise process and requires a multidisciplinary approach. A clinical geneticists/genetic counsellor should do the family work-up, genetic counselling and coordinate genetic testing. Genetic testing (microsatellite instability (MSI) and mismatch repair (MMR)-gene testing) should be done in an experienced molecular laboratory, preferably linked to the Clinical Genetics Section. Histopathologists are involved in immunohistochemical staining (IHC) to identify absence of MMR-proteins and should have experience in this field. Surgeons and/or gastroenterologists should perform surveillance colonoscopies on affected individuals and increased risk family members. Annual colonoscopy is advocated for MMR-gene carriers in Lynch syndrome/ HNPCC, as well as in individuals who has MMR-protein loss on IHC or a high number of unstable microsatellites in their tumour tissue in the absence of a MMR germline mutation. The risks and costs of colonoscopy should be explained to patients and family members. Oncologists should manage and treat all affected individuals and should help in coordinating follow-up surveillance colonoscopies in affected individuals. The flow diagram below (**Fig 1.2**) illustrates how patients and families at risk for inherited colorectal cancer should be managed.



MSI- microsatellite instability testing, MSH-microsatellite instability –high- indicates high amount of unstable microsatellites in tumour tissue, IHC- immunohistochemical staining to identify absence of MMR proteins, MMR- mismatch repair genes genetic testing, Amsterdam- Amsterdam revised criteria **(Table 1.4)**, Bethesda-Bethesda revised guidelines **(Table 1.5)**, ?IHC- can do immunohistochemical staining first to direct MMR gene testing or test the MMR genes directly if families are Amsterdam criteria positive, loss- loss of MMR-proteins detected with IHC

Figure 1.2 Genetic work-up and management of Lynch syndrome/HNPCC

1.2.5.3.2 Familial adenomatous polyposis (FAP)

A clinical diagnosis of familial adenomatous polyposis (FAP) is made if there are multiple polyps present on colonoscopy (100-200 polyps) (reviewed in Cole and Sleightholme, 2000). Classical FAP is therefore defined when more than 100 polyps are found in the colorectum at endoscopy or on pathological examination of the colon after colectomy. The prevalence in European populations appears to be 1: 8500, while the incidence appears to be 1.3 new cases per million population per year (reviewed in Firth, et al. 2005). Genetic testing is indicated in all individuals who are considered to have FAP, because the condition is dominantly inherited and due to mutations in the *APC* gene on chromosome 5q 22.2. The new mutation rate is estimated at 10-30% (reviewed in Firth, et al. 2005). Some cases are also due to autosomal recessive inheritance of mutations in a relatively recently described gene know as *MYH*, a DNA repair gene on chromosome 1p34.1 (reviewed in Firth, et al. 2005). No family history is seen in the latter cases usually and it is estimated that in European populations 25% of cases with more than 9 adenomas and no family history are due to *MYH* mutations (reviewed in Firth, et al. 2005).

An attenuated form of FAP (AFAP) (less than 100 colonic adenomas) has been described, with a later onset of colorectal cancer (usually over the age of 40 years). This form is more prevalent in the Ashkenazi Jewish population. A missense mutation in this population in the *APC* gene (I1307K) has been associated with this AFAP-like phenotype. An additional locus in the Ashkenazi Jewish population on chromosome 15q13-q22 has also been described and is known as *CRAC1* (reviewed in Firth, et al. 2005). *CRAC1* is responsible for hereditary mixed polyposis colorectal cancer, which is different from AFAP/FAP. There are a considerable

number of individuals and families with < 100, but more than 2 adenomas and multiplicity of adenomas is associated with a significant increase risk of colorectal cancer (Firth, et al. 2005). These patients/ families can be grouped under the term 'attenuated FAP' if other inherited colorectal cancer syndromes are excluded.

Clinical examination of individuals with multiple colonic polyps is important because FAP and some of the rare hamartomatous polyposis syndromes are multisystem diseases with many clinical features outside the gastrointestinal tract that are helpful in making the correct diagnosis. These extracolonic manifestations may also have serious consequences for affected individuals and they need to be monitored, screened and examined for them regularly, for example surveillance for papillary thyroid cancer and brain tumours in FAP. It is also important to distinguish other polyposis syndromes from FAP by examining patients for clinical features associated with the rarer polyposis syndromes and reviewing histopathology reports to identify the histological characteristics associated with each of the polyposis syndromes and thereby making sure that the correct diagnosis is made. Gardner syndrome is a term used for FAP with extracolonic manifestations, i.e. osteomas of the cranium, mandible and skeleton, multiple epidermoid cysts, fibromas of the skin, dental abnormalities and desmoid tumours of the abdominal wall (Lynch, Shaw, Lynch, 2004). Gardner syndrome is due to mutations in the *APC* gene (Baglioni and Genuardi, 2004). Careful clinical assessment of all colorectal cancer cases by a clinical geneticist is therefore important.

1.2.5.4 Colorectal cancer surveillance

There are important published surveillance recommendations for cancer in these syndromes. An example of this is annual colonoscopy advocated for gene carriers in HNPCC (Lynch et al. 2004). The benefit of regular colonoscopy has been shown through a controlled clinical trial extending over 15 years (Jarvinen, Aarnio, Mustonen, et al. 2000). Surveillance for cancer in for example HNPCC families should start at an early age (21 years). Annual full colonoscopy is also indicated if there is strong clinical evidence of HNPCC without genetic confirmation (Lynch, et al. 2003) (**Figure 1.2, section 1.2.5.3.1.3**). Surveillance in FAP needs to start at a much earlier age of 10-12 years in children at 50% risk for the condition or in gene carriers. The surveillance guidelines for early detection of colorectal adenomas and cancer in patients and family members at risk are listed in **Table 1.6** (http://www.cancer.org/docroot/home/index.asp).

Table 1.6 : American Cancer Society guidelines on surveillance for the early detection of colorectal adenomas and cancer in women and men at risk :

Risk category	Age to begin	Recommendation	Comments
INCREASED RISK			
People with a single, small (< 1 cm) adenomas	3-6 years after the initial polypectomy	Colonoscopy[1]	If the exam is normal, the patient can thereafter be screened as per average risk guidelines.
People with a large (1 cm +) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change.	Within 3 years after the initial polypectomy	Colonoscopy[1]	If normal, repeat examination in 5 years; If normal then, the patient can thereafter be screened as per average risk guidelines.
Personal history of curative-intent resection of colorectal cancer	Within 1 year after cancer resection	Colonoscopy[1]	If normal, repeat examination in 3 years; If normal then, repeat examination every 5 years.
Either colorectal cancer or adenomatous polyps, in any first-degree relative before age 60, or in two or more first-degree relatives at any age (if not a hereditary syndrome).	Age 40, or 10 years before the youngest case in the immediate family, whichever is earlier	Colonoscopy[1]	Every 5-10 years. Colorectal cancer in relatives more distant than first-degree does not increase risk substantially above the average risk group.
HIGH RISK			
Family history of familial adenomatous polyposis (FAP)	10-12 years	Early surveillance with endoscopy, and counselling to consider genetic testing	If the genetic test is positive, colectomy is indicated. These patients are best referred to a center with experience in the management of FAP.
Family history of hereditary non-polyposis colon cancer (HNPCC)	Age 21	Colonoscopy and counselling to consider genetic testing	If the genetic test is positive or if the patient has not had genetic testing, every 1-2 years until age 40, then annually. These patients are best referred to a center with experience in the management of HNPCC.
Inflammatory bowel disease Chronic ulcerative colitis Crohn's disease	Cancer risk begins to be significant 8 years after the onset of pancolitis, or 12-15 years after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia	Every 1-2 years. These patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease.

[1]If colonoscopy is unavailable, not feasible, or not desired by the patient, double contrast barium enema alone, or the combination of flexible sigmoidoscopy and double contrast barium enema are acceptable alternatives. Adding flexible sigmoidoscopy to double contrast barium enema (DCBE) may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic exam fails to reach the caecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion, or does not adequately visualize the entire colorectum.

1.2.5.5 Importance of surveillance

Genetic confirmation of an inherited syndrome is the ideal, but surveillance strategies cannot be withheld from individuals/ families who have strong clinical evidence of an inherited syndrome and who do not have affordable easy access to genetic testing. In South Africa where there is no readily available molecular diagnostic service for inherited colorectal cancer in all areas and at all levels of care, patients and families need to be clinically assessed, diagnosed and managed according to their inherited risks with appropriate surveillance stategies.

1.2.5.6 Inherited colorectal cancer risk assessment for genetic counselling

Risk assessment criteria were developed that categorise individuals and families into three different risk levels for colorectal cancer to decide who needs a genetic assessment and genetic counselling; high-, moderate- and average risk (**Table 1.7 and 1.8**). (Hampel, Sweet, Westman, et al. 2004). These criteria are used to assess who need to be referred to cancer genetic services and are not the criteria that are used to make a clinical diagnosis of an inherited cancer syndrome, for example the Amsterdam criteria for Lynch syndrome (**Table 1.3 and 1.4**) or the criteria used to decide who needs further genetic testing, for example the Bethesda criteria (**Table 1.5**) for Lynch syndrome.

1.2.5.6.1 High risk

Table 1.7 Risk assessment criteria for the high risk group (Hampel, et al. 2004).

HNPCC	-Three or more 1st/2nd degree relatives affected with any of the HNPCC associated cancers and include colorectal, endometrial, stomach, ovary, small bowel, billiary tree, pancreas, ureter and renal pelvis cancer (all cancers can occur in one generation with no age restriction). -One 1st degree relative/ 2nd degree relative has 2 or more HNPCC associated cancers at the same time (synchronous) or at different times (metachronous) -One first degree relative had colorectal cancer and was younger than 50 years at diagnosis.
Polyposis	- 1st or 2nd degree relative with > 10 polyps

Individuals in the high-risk category therefore have clinical characteristics and/or family histories highly suggestive of one of the hereditary cancer susceptibility syndromes. These individuals and their families would benefit from referral to a cancer genetics professional, increased cancer surveillance and genetic testing. Guidelines are available and were followed in this study regarding the management of individuals who are at high inherited cancer risk (Winawer, Fletcher, Rex, et al. 2003) and the surveillance recommendations are similar to **Table 1.6.** Not only cancer screening initiation, but also treatment strategies may be affected if there is an inherited risk. The treatment strategies are beyond the scope of this study. The

pathology and histological appearance of polyps are important in diagnosing one of the rarer polyposis syndromes and this also needs to be evaluated during the cancer genetic consultation.

1.2.5.6.2 Moderate risk

Table 1. 8 Risk assessment criteria for the moderate risk group (Hampel, et al. 2004)

Colorectal cancer risk	-One 1st degree relative with colorectal cancer diagnosed > 50 years and one 2nd degree relative with colorectal cancer at any age -Two 2nd degree relatives with colorectal cancer after the age of 50 years.

Individuals in the moderate risk category have a history which cannot be classified into the high risk category, but which still confers an increased risk for cancer, requiring increased cancer surveillance depending on the history (**Table** 1.6) (Hampel, et al. 2004).A cancer genetic consultation and increased surveillance of the colorectal tract are therefore also indicated in the moderate risk group.

1.2.5.6.3 Average risk

Average risk is where clinical and pathological characteristics and histories are not suggestive of an increased cancer risk as listed in the tables above. Increased cancer surveillance in this

category is unnecessary above the recommendations for the general population. Average risk is therefore a risk that is equal to the population risk for colorectal cancer. Surveillance recommendations also exist for this group of patients and are indicated from the age of 50 years in men and women according to American Cancer Society guidelines (www.cancer.org).

1.2.5.7 Genetic testing of inherited colorectal cancer

Genetic testing is important because the diagnosis of an inherited colorectal cancer syndrome can be confirmed in individuals who test positive for a germ-line mutation. These patients can then be targeted for specific cancer prevention strategies that may include prophylactic surgery or medical treatment. Family members that are at risk can then be offered predictive genetic counselling and testing for the germ-line mutation that was found in the affected family member. If they test positive, they can be targeted for the specific cancer prevention strategies related to the inherited syndrome. Individuals or family members that test negative can be reassured that they are not at increased risk and that less stringent screening recommendations can be followed and that surgical intervention is unnecessary.

It has been shown that genetic testing and counselling significantly influence the use of colonic endoscopy and adherence to recommendations for colorectal cancer screening in patients with hereditary non-polyposis colorectal cancer (HNPCC) (Hadley, et al. 2004). It has also been shown that mutation carriers were significantly more likely than test decliners to have colonoscopy (Halbert, Lynch, Lynch, et al. 2004). Research studies have evaluated the use of certain medications, for example non-steroidal anti-inflammatory drugs (NSAIDS), to reduce the colorectal cancer risk in the population and showed that there may be a benefit

(Smalley, Ray, Daugherty, et al. 1999). There is therefore an urgent need for a molecular genetic diagnostic service in the management of the inherited colorectal cancer syndromes in our population.

A diagnostic laboratory genetic service is currently not available in Johannesburg, Gauteng for inherited colorectal cancer. Genetic testing for familial adenomatous polyposis (FAP) is currently available on a research basis at the University of Stellenbosch, Western Cape. Limited diagnostic genetic testing for hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome was available until recently in the Western Cape at the University of Cape Town (personal communication, R Ramesar, Medical Genetics, University of Cape Town). A common mutation was found in one of the mismatch repair genes (*MLH1*) in a large family of mixed ancestry of the Cape Province, South Africa (Ramesar, Madden, Felix, et al. 2000) and testing was done on relatives at risk. Genetic testing is also now available for HNPCC at this centre for other population groups. The service is expanding and microsatellite instability testing and immunohistochemistry with subsequent germ line genetic testing of the mismatch repair genes is now available for Bethesda positive colorectal cancer patients/families (personal communication, R Ramesar, Medical Genetics, University of Cape Town). A diagnostic genetic service (microsatellite instability testing and mismatch repair genetic testing) for inherited colorectal cancer does not exist in Gauteng Province and testing is currently only available on a research basis at the Genetics Department of the University of Pretoria.

1.2.5.8 Population screening for inherited colorectal cancer

Screening needs to be user-friendly, reliable, cost-effective and sensitive. It can also only be successful if there is a definite management protocol (Winawer, et al. 2003) for the condition that is screened. The Wilson and Junger framework for evaluating screening tests/programs in a 1968 World Health Organisation (WHO) report is still used today for the evaluation of screening programs at population level (Wilson, 1968) (Goel, 2001). Criteria have been appraised for population screening in the context of testing for the genetic susceptibility for colorectal cancer, and only some of the criteria for population screening at this stage are met for this condition in developed countries. These include the following: the burden of colorectal cancer is significant, the ability exists to identify the target population, there is a considerable risk in the latent or preclinical phase of the disease, the natural course from premalignant adenomatous polyps to malignant polyps is understood and there is emerging consensus on the management of mutation carriers (Goel, 2001).

Criteria that are not met for population screening of colorectal cancer susceptibility in the developed world include: the acceptability of familial assessment and mutation testing in the general population is not yet established, the complete range of services required for genetic screening are not yet in place at population level (these should include facilities and infrastructure for adequate surveillance, prevention, treatment, education, counselling and social support at population level), the cost effectiveness in economic, psychological, social and medical terms is not yet established, familial assessment and testing are only available in specialized centres and the appropriate confidentiality procedures and antidiscrimination

provisions for participants and non-participants are not yet established (Goel, 2001). In the developing world and in South Africa these criteria are further away from being accomplished because in South Africa diagnostic genetic testing for colorectal cancer is not even available in most of the specialized centres.

At this time, the use of germ-line mutation testing to identify genetic susceptibility to colorectal cancer is certainly not recommended as a screening measure in the general population. The rarity of mutations in the APC- and HNPCC-associated mismatch repair (MMR) genes, and the limited sensitivity of current testing strategies, renders general population screening potentially misleading and not cost effective. High risk patients need to be identified, counselled and examined before molecular genetic testing is offered. Developing an effective inherited cancer program and creating awareness of the availability of cancer genetic counselling services is a priority before molecular diagnostic services can be developed.

1.3 Motivation for study

The threat of direct to consumer access of genetic testing and the request of genetic tests for inherited cancer by professionals without adequate genetic counselling, formal pedigree and histopathology analysis, risk estimation, management and follow-up are serious issues in South Africa today. There is also a lack of awareness of genetic counselling services. Wrong or mis-diagnosis because of incomplete family information and histopathological confirmation, inappropriate referrals and cancer genetic testing without proper counselling and follow-up are all threats to the delivery of adequate professional services for individuals and families at risk for an inherited cancer syndrome.

This study's primary motivation was to prevent mismanagement of patients and families at risk for inherited colorectal cancer by the development of a step-wise genetic counselling program for the identification and management of these patients and families and the assessment of a research tool for identifying high risk families. This step-wise program therefore makes a formal pedigree study essential and directs and standardises management and genetic testing in all patients and families who were found initially to be at increased risk for inherited colorectal cancer. Genetic assessment and counselling offers the potential to focus cancer surveillance on individuals truly at increased risk, thereby reducing mortality, morbidity and costs. It also offers the potential to focus genetic testing on individuals truly at high risk and on individuals who are well informed and who make a choice if they want genetic testing to be undertaken. Through this program it is hoped that inappropriate genetic

testing will in future be prevented on moderate and average risk individuals and on individuals that do not want genetic testing to be undertaken for various personal reasons.

The final outcome of the project was to develop a genetic counselling program for inherited colorectal cancer. It is hoped that in future the program could be expanded and that a more comprehensive program for all the inherited cancers can be instituted at all levels of care to improve the identification, counselling, testing and management of patients and families at risk for inherited cancer.

1.4. Aims

1.4.1 Primary aims

The development of a step-wise genetic counselling program for inherited colorectal cancer. This was achieved by:

1) *Drawing up a personal and family history questionnaire as a tool for the initial identification of increased risk families.*
2) *Classifying patients/families into one of three risk categories for inherited colorectal cancer (average, moderate and high risk).*
3) *Managing research participants and families, from the genetic point of view, according to their risk.*

1.4.2 Secondary aims

The secondary aims were to:

- *Assess the reliability of the self-administered personal and family history questionnaire used in this study in risk stratifying patients/families.*
- *Increase cancer genetic referrals to the Division of Human Genetics at the University of the Witwatersrand and National Health Laboratory Service*
- *Establish a multidisciplinary service for the management of families at increased risk for colorectal cancer.*
- *Create awareness in the health care professionals associated with the practices/clinics used in this study of the availability and importance of genetic counselling and genetic testing in the basic management of inherited cancer risk.*
- *Create awareness of the urgent need for cancer genetic molecular diagnostic services in Johannesburg.*
- *Assess patients' and families' attitudes towards the genetic counselling program and their response to genetic counselling and genetic testing.*
- *Assess patients' feelings regarding the sharing of cancer risk information with their relatives.*

2. STUDY DESIGN, SUBJECTS AND METHODS

2.1 Introduction

This section will discuss the study design and period under which the study was undertaken, the recruitment and selection of study participants, the construction of the consent form and information sheet for patients, assent form for minors (<18 years), research tool (personal and family history questionnaire), standard letter for average risk participants and cascade letter for family members at increased risk of colorectal cancer. A discussion will then follow describing the distribution of the consent form, information sheet and research tool (personal and family history questionnaire) to patients affected with colorectal cancer, the procedure for data collection and the management of participants and families according to their genetic risk. The methods of how the quantitative calculations and observations were made from the collected data are then discussed. A statement on ethics approval for the research project will end this chapter.

2.2 Study design

The study, undertaken over a 28 month period, from May 2005 to August 2007, was a prospective observational study that assessed the effectiveness and benefits of using a newly developed step-wise genetic counselling program to identify, test and manage individuals/families at risk for inherited colorectal cancer. No similar standardized program or South African guideline is available for comparison.

Observations that were made to evaluate the effectiveness and benefits of the program were to see if:

- The patient-based self-administered data collection tool linked to an information sheet and consent form used in the first step of the program was reliable in collecting information for risk stratification of families.
- Patient numbers increased after institution of the program,
- Awareness was created of the availability of cancer genetic services
- Patients and families accepted the program
- The program led to the establishment of a multidisciplinary surveillance and follow-up service for at risk patients and families.
- Patients were happy to share their risk information with their relatives.

2.3 Participant selection

- *Study sample*- a consecutive group of forty-eight newly diagnosed and follow-up patients seen at various clinics across Gauteng Province, South Africa, affected with colorectal cancer was approached and handed questionnaires by the specialists and staff working at these clinics. Those patients that volunteered and completed and returned the questionnaires became study participants. All the patients that completed the questionnaire and signed consent became study participants. No-one who was approached refused to participate.
- *Participant recruitment*- patients were recruited from specialist clinics and specialist private practices where they are surgically managed and medically treated for

colorectal cancer. The specialists at these practices/clinics that are routinely involved in management and treatment of patients with colorectal cancer include oncologists, gastroenterologists and surgeons. The self-administered questionnaire the writer developed could not be instituted at population level or considered a screening tool because of the absence of a definite management protocol at a population level (Winawer, et al. 2003) and the fact that genetic counselling professionals currently do not know the acceptability of familial assessment and genetic testing in the general South African population. It was therefore only aimed at a target population already affected with colorectal cancer at tertiary level in a few selected practices in Gauteng where the colorectal patient load was expected to be high. It is a pilot project to evaluate if a research tool with follow-up counselling was successful in identifying and managing increased colorectal cancer risk patients before a large scale family cancer program can be instituted at population level.

- *Practices/clinics/wards chosen for patient recruitment-* the clinics and practices that were used included Johannesburg General Hospital Medical Oncology Clinic, Gastroenterology Clinic and General Surgery Ward, Donald Gordon Medical Centre Medical Oncology Practice in Johannesburg, Little Company of Mary Hospital Medical Oncology Practice in Pretoria, and a specialist surgery outpatient practice at Milpark Hospital in Johannesburg. Patients that contacted our department who wanted to arrange an appointment to discuss inherited risks for colorectal cancer were also included.
- *Motivation for using the specified practices/clinics/wards-* Six practices/clinics were chosen in Gauteng and it was limited to this number because it was intended to be a pilot project. Both the private oncology practices that were used are linked with

Medical Oncology at the University of the Witwatersrand and the University of Pretoria respectively. Permission for recruitment at the oncology practices was obtained from the Head of Medical Oncology at Johannesburg Hospital, Prof Paul Ruff and the Acting Head of Medical Oncology at Pretoria Academic Hospital at the time, Dr Coenraad Slabber. The gastroenterology clinic and general surgery ward were the only other clinics/wards that were approached at Johannesburg Hospital because this is where most of the newly diagnosed colorectal cancer patients are primarily managed. The surgery practice at Milpark hospital that participated in the research is linked to the surgery unit at Johannesburg Hospital. Patients who contacted the Division of Human Genetics in Johannesburg were included because the program was also aimed at assessing personal and family history information of self-referring patients for risk stratification, genetic testing and management.

2.4 Construction of information sheet, consent form, research tool, standard letter for average risk participants and cascade letter

2.4.1 Information sheet and consent form for patients (Appendix 2a)

An information sheet and consent form was constructed. The first paragraph included a greeting, an introduction of the study investigator, his affiliation and an invitation to take part in the research project.

The second paragraph stated the aim of the research project. It informed participants that there was a multidisciplinary service planned and that they would be managed according to international standardised protocols for the purpose of cancer prevention in themselves and their family members.

The third paragraph stated how much of the participants' time is needed to complete the questionnaire and how he/she could complete and return the questionnaire to the investigator. A fax number was given if the participants' wanted to fax the questionnaire to the investigator. The investigator also asked the participants' permission to access their medical records.

A fourth paragraph was constructed that stated that all the information would be treated confidentially and that the participants' treatment would not be affected in any way should they decline to participate or should they choose to withdraw from the study.

A fifth paragraph stated the procedure that would take place should the participant be found to be at increased risk for inherited colorectal cancer.

A final paragraph with a space for the participants' signature, a date and a space and a date for the signature of a witness in case of verbal consent was included for the purpose of consent. The investigator's contact numbers were included if there were any questions or if the participant had any problems with interpretation of the questionnaire.

2.4.2 Information sheet and consent form for parents (Appendix 2b)

A information sheet and consent form for parents was constructed on the same principles explained in section 2.2.2. This was constructed for parents of minors who participated in the research project. The same information discussed in section 2.4.1 was included.

2.4.3 Assent form (Appendix 2c)

An assent form for minors (< 18 years) was constructed and included a greeting, introduction and simple explanation of the purpose of the research project to the minor. A paragraph stating that there would be some questions that their parents need to fill in on a questionnaire, that there would be an examination on them and that their medical records would be used was constructed. A final paragraph stating that the study would not benefit them directly, but that it may benefit their family members was also constructed. A sentence asking for a verbal agreement from the minor to participate in the study was included at the end of the assent form.

2.4.4 Research tool- personal and family history questionnaire (Appendix 3)

Family history data collection tools are used in some cancer genetic clinics in the United States, Europe, Canada and Australia to overcome the problem of inadequate family cancer histories recorded by clinicians in busy oncology and specialist clinics. This may take the form of a computer based data collection tool (Acheson, et al. 2006) or a printed questionnaire, e.g. the West Midlands Family Cancer Strategy, United Kingdom (reviewed in Cole,

Sleightholme, 2000). A self-administered, computerized tool for collecting a family history of cancer was validated and the test-retest reliability was found to be high (Acheson, et al. 2006). In South Africa, we currently do not have expensive technology available to institute a computer based questionnaire at tertiary health care settings, most private practices and at State hospitals in South Africa. The writer developed a patient-based self- administered printed questionnaire as a data collection tool as it was thought to be more appropriate in the South African setting. The printed questionnaire also gave participants the opportunity to discuss family cancer histories with their relatives at home in their own time before returning it to their specialist, which may have increased the accuracy of the information.

A family cancer history questionnaire on first degree relatives was validated in two European centres through the Clinical Cancer Research Unit in Basel, Switzerland (Mussio, et al. 1998). The first part of the family history questionnaire constructed for this research project was based on the questionnaire used in the study of Mussio et al. (1998). Family history information provided on first degree relatives is however not adequate for inherited cancer risk stratification, as cancer histories in second degree relatives are also important to make a final risk assessment. The family cancer history questionnaire used in this research project was therefore further developed for the purpose of accurate risk stratification. The second part of the family history questionnaire on second degree relatives was constructed in the same format as the first part of the questionnaire and was based on the writer's clinical experience in the genetic counselling clinic. There is currently no evidence-based analysis available on the accuracy of family cancer history reporting in the South African medical literature.

The first page of the questionnaire consisted of the demographic data. Questions regarding the participants' first and middle names, family name/surname (maiden name in case of females) and married name were included. The participants' street and postal address, contact and fax numbers, e-mail address and contact numbers of his/her close relatives were included. A female participants' family name (maiden name) could help in linking families who have colorectal cancer. A space for a patient code was left on the first page to link it to the rest of the questionnaire if this page were detached. This was for future use when genetic testing of the histopathology samples is done for the purpose of confidentiality.

A personal information sheet on the second page of the questionnaire was constructed and consisted of the current date, the participant's current age, sex, occupation and race. A space for the participant's study code was constructed. This will be used in future when genetic testing of the histopathology/ blood samples are done for the purpose of confidentiality. This part of the questionnaire with the family history section can be removed from the first page of the questionnaire when genetic testing is done in the laboratory. A personal cancer history section on the participant was also included here. The type of cancer the participant had, the age of onset of his/her cancer, the histology and the site of cancer and if there were any other malignancies in the past was noted. This information is valuable in assessing inherited risk and it is based on the writer's experience in the genetic counselling clinic. A statement at the top of this page was included stating that this section of the questionnaire was confidential and that it would not be shown to anyone, except to the researcher and his supervisor.

2.4.5 Standard letter for average risk participants (Appendix 4)

A standard letter was constructed and sent to all participants who fell into the average risk category. This letter thanked them for their participation and it stated that their family members were at the average population risk for colorectal cancer according to the information they provided in the questionnaire. The international population guidelines for average colorectal cancer risk were stated in this letter (www.cancer.org/ American Cancer Society). The letter also stated that families should notify staff at the Genetic Counselling Clinic if any changes arise in future in their family history information regarding cancer, as this may alter their risk classification. A paragraph stating the management guidelines for people who have a personal history of colorectal cancer was included for the affected study participants. Contact numbers and fax numbers of the investigator and the Genetic Counselling Clinic were included should the study participants require any further information.

2.4.6 Cascade letter for family members at increased risk of colorectal cancer (Appendix 5)

A cascade letter for family members at increased risk of colorectal cancer was constructed. This letter was sent to family members via the proband. This letter consisted of a basic explanation of inherited colorectal cancer and the risks involved. It also included a paragraph explaining autosomal dominant inheritance with a final sentence stating that doctors would be able to advise them about measures to screen and possibly prevent cancer. Contact numbers of five professionals that work in the Genetic Counseling Clinic at the National Health

Laboratory Service in Johannesburg were included as well as the contact number of the secretary at the Clinic. A sentence stating that a consultation with genetics professional would put the family member under no obligation to undergo a genetic test was also included in the final paragraph of the cascade letter.

The cascade letter gave the family members the opportunity to decide for themselves if they wanted to contact the staff at the Genetic Counselling Clinic to arrange a genetic counselling session. It remained the probands' responsibility to inform their relatives about their colorectal cancer risks and to hand out the cascade letters to them.

2.5 Data collection

2.5.1 Distribution of information sheet, consent form and research tool

The information sheets, consent forms and personal and family history questionnaires (research tool) were distributed sequentially to all patients who were newly diagnosed with or were followed-up for colorectal cancer. The distribution was done by the treating specialists after the patients' appointments or by their staff members after their specialist appointment. The questionnaires were also distributed to surgical in-patients at Johannesburg Hospital by staff members, interns, registrars or consultants. Private practices/clinics/ wards that were involved were informed about the procedure to distribute the questionnaires.

2.5.2 Procedure for data collection

A **three-step approach** was followed to identify, enroll in the study, risk stratify, counsel, test and manage patients and their families affected with colorectal cancer (**Appendix 1**).

2.5.2.1 Step-1

Doctors, their receptionists and nurses of cancer and gastroenterology services were approached to discuss the project and were asked to participate in referring patients to the study. Those patients who agreed to participate were asked to read an information sheet and sign a consent form if they were willing to participate (**Appendix 2**) and then complete a personal and family history questionnaire in their own time (**Appendix 3**). Patients could take questionnaires home to discuss cancer histories with their relatives or complete the questionnaires at the clinic/practice or in the ward. The completed questionnaires could be left at the specialist practice for collection or study participants could also fax or post the questionnaires to the Division of Human Genetics in Johannesburg.

If there were any problems with interpretation or understanding English, a translator from our clinical division (a research nurse) was available to help. Contact numbers were provided on the information sheet if help was needed or if patients had questions or wished to discuss aspects of their cancer.

Confidentiality was maintained throughout the program. The completed questionnaires were kept in a separate confidential file until collection at the specialist practices. Faxed or posted

questionnaires were addressed to the writer only and were directly handed to the writer by a secretary. Completed questionnaires were filed into individual patient files after the patient letters were sent out and kept in a locked filing room with controlled access. Access to patient's medical files at the specialist practices was restricted unless informed consent was signed by the study participants.

2.5.2.2 Step-2

Participants were classified by the writer according to their personal and family history information into one of three risk groups; average, moderate or high risk. The criteria used are listed in **Table 1.7** and **Table 1.8.** The criteria used were not aimed at identifying individuals or families that needed genetic testing, as the criteria are not sensitive enough. The criteria used were to identify patients/families that would benefit from a clinical genetic consultation, genetic risk counselling and surveillance.

If there were any uncertainties in the data that could influence the risk classification, patients were contacted telephonically to clarify the information.

Patients had an opportunity on the final page of the questionnaire (**Appendix 3**) to inform the writer of any information that they thought was valuable and of any questions they may have. They could also tell the writer about their/their families' anxieties regarding inherited cancer risk here. Patients who fell into an average risk category who needed more information or genetic counselling because of these comments or who had excessive anxiety were also given an opportunity to be seen.

2.5.2.3 Step- 3

Patients/families were phoned for an appointment at a place convenient to them if they were found to be at moderate or high risk. Patients who agreed to the clinical appointment were then interviewed, a formal pedigree study was done, histopathology reports were assessed and they were examined and counselled.

Each appointment was given an approximate time frame of one and a half hours to complete.

A detailed three-generation family tree was constructed and information was gained from medical files and histopathology reports regarding the microscopic appearance of tumours, the staging, surgery and the chemotherapy. This information was important because the cancer diagnosis and the family history information needed to be confirmed before patients and family members could be entered into a cancer surveillance program or offered genetic testing.

Specific genetic counselling techniques were used to address patients' anxieties and concerns regarding the inherited risks. Visual material was used to guide them through the process of understanding the genetic basis of colorectal cancer, the inheritance patterns and the familial risks. The writer addressed the psychosocial aspects and ethical issues related to inherited colorectal cancer, genetic testing and the sharing of genetic information with relatives and third parties.

The writer examined the affected study participants for clinical signs of the rarer familial gastrointestinal hamartosis/polyposis syndromes, looking specifically for growth abnormalities, developmental abnormalities and pigmented skin manifestations of these syndromes. The writer examined clinically for multi-system abnormalities related to familial adenomatous polyposis (FAP) if this condition was present. The writer also examined the skin for benign or malignant sebaceous skin tumours and keratoacanthomas, both important in HNPCC to diagnose a variant of this syndrome called Muir-Torre syndrome, which usually indicates mismatch repair gene mutations in specific mismatch repair genes (*MSH2 and MLH1*) and cutaneous and internal organ microsatellite instability. If central nervous system tumours were associated with colorectal cancer or colonic polyps, like glioblastoma mutiforme (in HNPCC) or medulloblastoma (in FAP), a diagnosis of Turcot syndrome needed to be considered, increasing the chance that a germline mutation may be present in that family.

During this interview, participants were informed about the inherited risks to their extended family and they were asked to inform their family members of these risks. They were also asked how they felt about sharing the risk information with their family. Participants' and families' attitudes towards the genetic counselling program and their responses to genetic counselling and genetic testing were assessed. Patients were asked how they felt about genetic testing and if they thought that they or their family members at risk would benefit from genetic testing. Reasons why they would pursue genetic testing were also sought. The writer noted their responses and their reasons in their files. This was done to give the writer some indication if the cancer program and subsequent genetic testing were needed from the particpants' perspective, if the program was well accepted and if it was to the participants' perceived benefit. The responses were recorded in a generalised way and were not

qualitatively assessed, specifically recorded word for word in the participants' files or taped for later revision, as this fell beyond the purpose of this research project. The writer could therefore only make a statement on his perceived impression of the participants' and families' responses in a generalised fashion.

The revised Bethesda criteria (**Table 1.5**) were used in our study to decide who needed to be considered for DNA extraction and banking of germ-line DNA for future genetic work-up. High risk patients who needed specialized tumour testing were therefore offered the opportunity to bank DNA at the molecular genetics laboratory, not only for future germ-line genetic testing of MMR genes, but also because normal DNA needs to be compared with tumour DNA when MSI testing is performed.

Tumour and germ-line genetic testing will be performed on all the high risk patients that were identified in this study who agreed to genetic testing. The testing will be performed at the Human Genetics Department of the University of Pretoria as a service to these patients. The results of the testing fall beyond the purpose of this research project.

Participants were sent a detailed information letter about the genetic consultation and the discussions. This letter had information about the family history, the tumour pathology, the clinical assessment, the genetic counselling and ethical issues, information on the genetic risks to relatives and information if genetic testing was indicated and if DNA was extracted and banked. A detailed management program with information about the frequency of special investigations for colorectal cancer screening and screening for associated cancers

(preventative cancer surveillance program) for the participants and their family members was also included in this letter. Copies of these letters were sent to their doctors.

The establishment of a multidisciplinary service for the management of patients was therefore accomplished in collaboration with the health professionals linked to the practices involved in this study. The management of these individuals and/or families was based on the most recent international guidelines of the National Institute of Cancer of the United States of America (www.cancer.org) for cancer risk reduction (**Table 1.6**). Risk reduction may include regular follow-up with clinical examinations and/or special investigations, medical treatment or surgery where indicated; therefore the need for a multidisciplinary approach. Long-term management of individuals and/ or families would also involve their primary care physicians, provided that they were informed of the appropriate further management.

2.6 Management of participants and families

Participants were managed according to their risk as summarised below:

- Average risk participants and families- a standard letter with population guidelines for colorectal cancer surveillance was sent (**Appendix 4**).
- Increased risk participants/families (moderate and high risk)
    a. Genetic counseling assessment with a formal pedigree study, histopathology report evaluation and clinical examination of affected proband.

b. Reclassifying participants/families into risk categories according to the data obtained from the formal pedigree study and clinical examination, informing them of their risks and counselling them regarding management guidelines and the indications for and availability of genetic testing.

c. Offering genetic testing if they were found to be at high risk and then banking their DNA and obtaining consent to do specialized genetic testing on their tumour tissue if they wanted to pursue the route of genetic testing.

d. Directing management of participants/families according to their risk with organ surveillance and sending follow-up information letters with surveillance guidelines to patients and their treating doctors and specialists.

e. Sending cascade letters to participants for their family members with risk information (**Appendix 5**).

2.7 Quantitative calculations and observations from collected data

- The risk classification obtained after the genetic counselling session was compared to the risk classification based on family history data in the questionnaires in the moderate and high risk groups. This was to see if the questionnaire was informative enough to be used as a tool to assess familial risk.
- Information in the personal history data section of the questionnaire was compared to information in patients' medical files and histopathology reports to assess how many patients in the moderate and high risk groups gave the correct information regarding their tumours and the age of onset of their cancers.

- The number of patients seen for genetic counselling as a percentage of the total number of patients that participated in the study was calculated.
- The number of patients who were interested in genetic testing and banking their DNA for genetic work-up in the high risk group was calculated.
- The increase in patient numbers seen for inherited colorectal cancer at the Clinical Section of the Division of Human Genetics at the National Health Laboratory Service and the University of the Witwatersrand was calculated. Patient figures since starting the program in 2005 until completion in 2007 were compared to figures seen over a similar time span in previous years (approximately 2 years, from 2003-2005).
- Observations regarding the patient's attitudes towards genetic counselling, genetic testing, further management of their/their families' inherited risks and the need for a multidisciplinary service were done during the genetic counselling sessions and the number of patients who were positive about these points were calculated in the moderate and high risk groups.
- The number of patients in the moderate and high risk groups who were positive about sharing cancer risk information with their families was calculated.

2.8 Ethical considerations

Ethics approval for the research project was received from the Human Ethics Research Committee in 2005. The ethics clearance number is R14/49, protocol number M050227 (**Appendix 8**).

3. RESULTS

3.1 Patient participation and risk stratification

Forty eight (48) completed questionnaires were received in a 25 month period from the time data collection started. The first questionnaires were completed in May 2005 and the last questionnaires included in the study were completed in May 2007. Participants were clinically assessed and counselled from September 2005 until August 2007 (28 months).

On the basis of the questionnaire, thirty-three (33) families (69%) were assessed to be at increased risk (moderate or high risk) and 15 families (31%) were assessed to be at average risk for an inherited colorectal cancer syndrome (**Table 3.1**). Just more than two thirds of patients/families that participated in the study were therefore found to be in a risk category (moderate or high risk) where a clinical genetic assessment with genetic counselling was indicated.

There were 28 males (58%) and 20 females (42%) that participated in the study (**Table 3.2**). Forty two (42) (88%) of the total number of 48 participants were white (25 males and 17 females) and of this group of participants, 24 (50% of total participants) were Afrikaans speaking individuals, 15 (32%) were English speaking and 3 (6%) were Ashkenazi Jewish (**Table 3.2**). Most of the participants came from Gauteng province (43) (90%). Four participants (8%) were from other provinces in South Africa and one participant (2%) was not a South African citizen (**Table 3.2**). Most of the participants were employed or self-employed, had medical aid and were from various sectors of society (34) (71%). Seven of the participants

were pensioners (14.5%) and 7 were housewives (14.5%) (**Table 3.2**). The age range of participants that fell in the average risk category was 52-73 years and the age range of those that fell into the increased risk category was 27-78 years. The mean age for the average risk group was 61 years (SD ±5) and the mean age for the increased risk group was 49 years (SD±13). None of the participants was under the age of 18 (**Table 3.2**).

The 48 patients/families that participated in the study were recruited from various private practices, hospital clinics and wards as well as from telephonic enquiries to the Division of Human Genetics. The patient participation according to recruitment site as well as according to population group is summarized in **Table 3.3.**

Table 3.1 Completed questionnaires and risk stratification

Completed questionnaires	Number	Percentage (%)
Total	48	100%
Increased risk (moderate/high risk)	33	69%
Average risk	15	31%

Table 3.2 Demographic data

Demographic data	Total participants	48	Percentage
Sex	Male:	28	58%
	Female	20	42%
Population group	**Black:**	**2**	**4%**
	Male	0	
	Female	2	
	Indian:	**2**	**4%**
	Male	1	
	Female	1	
	Coloured:	**2**	**4%**
	Male	2	
	Female	0	
	White:	**42**	**88%**
	Male	25	
	Female	17	
	-White Afrikaans:	24	50%
	-White English:	15	32%
	-Ashkenazi Jewish:	3	6%
Address	**Gauteng:**	**43**	**90%**
	-Johannesburg North:	10	
	-Johannesburg South:	2	
	-East Rand:	3	
	-Centurion:	2	
	-Pretoria East:	20	
	-Pretoria West:	2	
	-Pretoria North:	2	
	-Pretoria Central:	1	
	Other provinces:	**4**	**8%**
	-Northern Province:	3	
	-Free State Province:	1	
	Other countries:	**1**	**2%**
	-Nigeria:	1	
Occupation	Employed/self-employed:	34	71%
	Pensioner:	7	14.5%
	Housewife:	7	14.5%

Age range- Average risk	52-73 years	
Increased risk	27-78 years	
Mean age- Average risk	61 years (SD± 5)	
Increased risk	49 years (SD±13)	
Age < 18 years	0	

Table 3.3 Patient participation according to recruitment site

Recruitment site	Number of patients	Percentage
Mary Potter Oncology Centre Pretoria	31	65%
Donald Gordon Medical Centre Oncology Johannesburg	5	11%
Milpark Surgery Practice	4	8%
Telephonic enquiries	3	6%
Johannesburg Hospital Medical Oncology Ward	2	4%
Johannesburg Hospital General Surgery Ward	2	4%
Johannesburg Hospital Gastroenterology Clinic	1	2%
Total	**48**	**100%**

3.2 Clinically assessed cases

Twenty-nine affected probands from the 33 increased risk families (moderate or high risk) that were risk stratified from data obtained in the questionnaires were clinically assessed and counselled at completion of the study by the end of August 2007 (**Table 3.4**).

Affected study participants/probands of 4 increased risk families (12%) were therefore not seen. These patients/families could not be seen for the following reasons:

- One proband was undergoing chemotherapy in 2007 and cancelled the appointment twice.
- One proband passed away before the genetic counselling appointment date.
- One proband did not leave any personal contact details or an address.
- One proband lived in another province in South Africa and could not arrange to come for the genetic counselling appointment because of travel problems.

Average risk affected probands were not clinically assessed and counselled. The 16 affected study participants at average risk were sent standard letters informing them of their genetic risks with surveillance guidelines. These letters stipulated that they are at general population risk for colorectal cancer and that the general population screening guidelines of the National Cancer Institute of America (www.cancer.org) for colorectal cancer (after the age of 50 years) apply to their first degree family members.

Table 3.4 Final number of clinically assessed cases

	Number	Percentage
Total number of study participants	48	100%
Increased risk families	33	69%
Increased risk: pedigree study, clinical assessment of proband and genetic counselling	29	60%

3.3 Accuracy of questionnaire data used in risk stratification of increased risk families

A formal pedigree study and a clinical assessment was done on 29 affected probands (**Table 3.4**) and it was found that 28 families (28/29) or 97% were correctly classified into their initial risk category assigned from the raw data obtained in the completed questionnaire (**Table 3.5**).

The one family (see family pedigree-1- **Figure 3.1**) that was incorrectly classified changed from moderate risk to average risk after confirmation that the type of cancer in one of the first degree relatives (prostate cancer) was not a HNPCC associated cancer (urogenital/kidney cancer) (Amsterdam II criteria- **Table 1.4**).

All 29 (100%) affected probands of the increased risk group (moderate and high risk) gave the correct personal information in the questionnaire regarding their cancer and the age of onset of their cancers when this information was verified with medical files and histopathology data (**Table 3.5**).

Raw data from completed questionnaires of average risk families could not be verified because a formal pedigree study with a clinical assessment and subsequent genetic counselling was only done on probands from families that were found to be at increased risk (moderate or high risk).

Table 3.5 Accuracy of questionnaire data in increased risk families assessed

	Number	Percentage
Pedigree studies and clinical assessments- total	29	100%
Familial risk classification accurate from questionnaire data	28	97%
Personal data correct	29	100%

3.4 Increased risk families- final risk assignment, clinical diagnosis and genetic testing

3.4.1 Final risk assignment

Of the 28 families that remained in an increased risk category (moderate/high risk) after the formal clinical assessment and pedigree study, 2 families (2/28) or 7% were at moderate risk and 26 families (26/28) or 93% were at high risk for an inherited colorectal cancer syndrome (**Table 3.6**). High risk indicates that the Amsterdam criteria (**Table 1.4**) or the Bethesda criteria (**Table 1.5**) were positive and that genetic studies are indicated.

Table 3.6- Final risk assignment, provisional clinical diagnosis and DNA banking

Risk classification/diagnosis	Number	Percentage
Increased risk families (moderate and high risk)- **final number after clinical assessment**	28	100%
High risk-**total**	26	93%
High risk- **Amsterdam** criteria positive	7	25%
High risk- **Bethesda** criteria positive	18	64%
High risk- **FAP**	1	4%
Moderate risk-**total**	2	7%
Features of hamartomatous polyposis syndrome	0	0%
Multisystem manifestations related to FAP/HNPCC	0	0%
DNA banked on proband	26	93%

3.4.2 Amsterdam criteria positive

Of the 26 high risk families, 7 (25%) families fulfilled the revised Amsterdam clinical criteria (**Table 1.4**) for hereditary non-polyposis colorectal cancer (HNPCC). A provisional clinical diagnosis of HNPCC was therefore made in these families (**Table 3.6**). The affected probands

in all 7 of these families are undergoing germ-line (blood lymphocyte) genetic testing for mismatch repair gene mutations. This is an ongoing service to these families and is being done in collaboration with a research laboratory.

3.4.3 Bethesda criteria positive

Eighteen (18) (64%) families (**Table 3.6**) were at high risk for HNPCC according to the revised Bethesda criteria (**Table 1.5**). The affected probands in these 18 families should have microsatellite instability (MSI) testing to determine if they have tumour characteristics of HNPCC. Immunohistochemistry (IHC) should follow in all positive MSI results to decide which genes to target (**Figure 1.2**). Germ-line genetic testing may then be indicated in patients should these tumour characteristics of HNPCC be present.

3.4.4 Familial adenomatous polyposis

In 1 family (4%) the affected proband had sufficient clinical criteria for a diagnosis of familial adenomatous polyposis (FAP) (> 100 polyps in colon on colectomy) (**Table 3.6**). Genetic testing for the *APC* genetic mutation on chromosome 5 on this family member is being performed in South Africa (as part of a research project of the University of Stellenbosch) and was also performed at an overseas laboratory in the Netherlands for diagnostic purposes. The University of Stellenbosch has not yet completed the testing at the time of writing up the research report. The Netherlands laboratory did not find a mutation on sequencing of the whole gene and further genetic testing for the recessive *MYH* genetic mutation for FAP is indicated (**Table 1.2**).

3.4.5 DNA banking

All the high risk patients (26) were offered the option of banking their germ line DNA for future genetic work-up. All high risk patients agreed to DNA banking and further genetic testing (**Table 3.6**).

3.4.6 Moderate risk

The two families who were at moderate risk (**Table 3.6**) needed advice on surveillance and screening on themselves and their family members. Further genetic testing was not indicated and DNA banking was not offered in this group because there is not enough clinical evidence for an inherited colorectal cancer syndrome, unless the family history changes in future.

3.4.7 Clinical features

None of the affected study participants clinically assessed in the increased risk families had any external features of one the hamartomatous polyposis syndromes (**Table 3.6**). There were also no multi-system manifestations related to the specific inherited colorectal cancer syndrome that was considered in the particular family (**Table 3.6**).

3.4.8 Family notification of risk

Cascade letters (**Appendix 5**) were sent to probands of all high risk families to distribute among the relatives at risk. The cascade letters are information sheets informing family members of their risks and inviting family members for genetic counselling.

3.5 Family pedigree examples illustrating risk classification

For clarification of the risk classification of **Table 3.6**, family pedigrees (anonymous) on the following four pages are included to illustrate an average risk family (**Figure 3.1**), a moderate risk family (**Figure 3.2**), one Bethesda criteria positive family (**Figure 3.3**) and one Amsterdam criteria positive family (**Figure 3.4**).

3.5.1 Family pedigree-1 (Average risk)

- **II-4** -Affected proband (arrow)- colorectal cancer at age 66 years
- **II-1** -Brother with prostate cancer at 65 years (died of prostate cancer) that was reported as kidney cancer in questionnaire- risk decreased to average risk when diagnosis of prostate cancer was confirmed in brother (prostate cancer is not a HNPCC- associated cancer).

None of the other relatives that died had cancer

Family assessed as average risk with no need for increased surveillance of relatives above population guidelines.

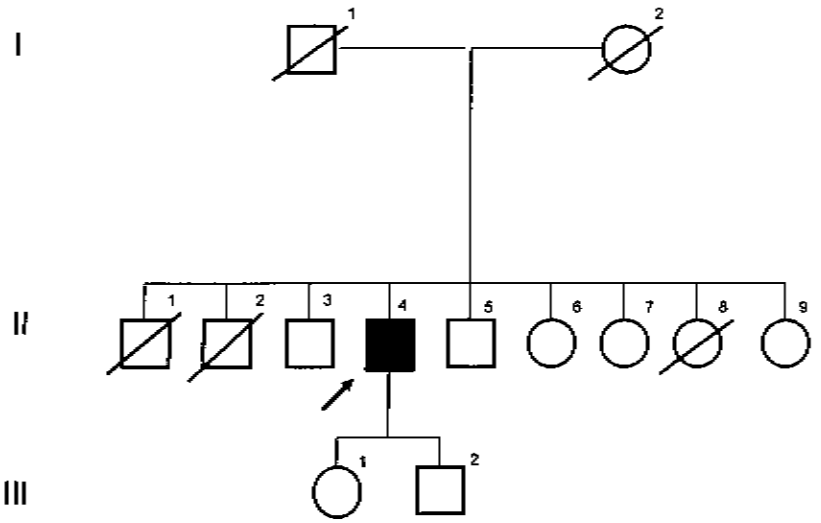


Figure 3.1 Family pedigree-1: Average risk

3.5.2 Family pedigree-2 (Moderate risk)

- **III-1**- Affected proband (arrow)- colorectal cancer at age 61 years
- **I-4** - Maternal grandmother of proband- colorectal cancer diagnosed at age 50 years- died of colorectal cancer

None of the other relatives that died had cancer

Increased surveillance is indicated in first degree relatives from the age of 40 years.

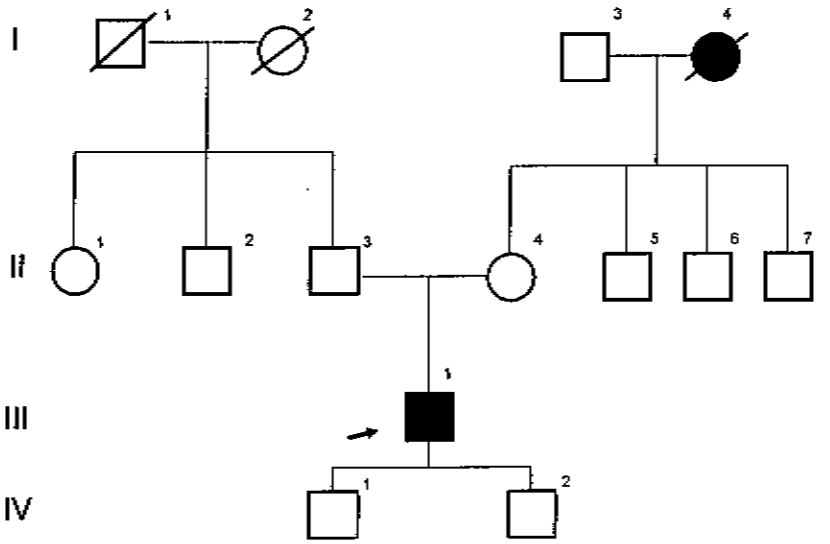


Figure 3.2 Family pedigree-2: Moderate risk

3.5.3 Family pedigree-3 (High risk- Bethesda criteria positive)

- **III-5**-Affected proband (arrow)- colorectal cancer diagnosed at age 55 years
- **II-3**- Father of proband- colorectal cancer diagnosed at age 46 years- died of disease
- **III-1**-Paternal first cousin of proband (3rd degree relative)- colorectal cancer at 39 years
- **II-4**-Mother of proband- breast cancer diagnosed at age 54 years- died of breast cancer
- **I-4**-Maternal grandmother of proband- stomach cancer diagnosed at age 65 years- died of stomach cancer
- **I-1**-Paternal grandfather of proband- died of cancer, but diagnosis was uncertain and could not be confirmed (not reported as colon cancer)

None of the other relatives that died had cancer.

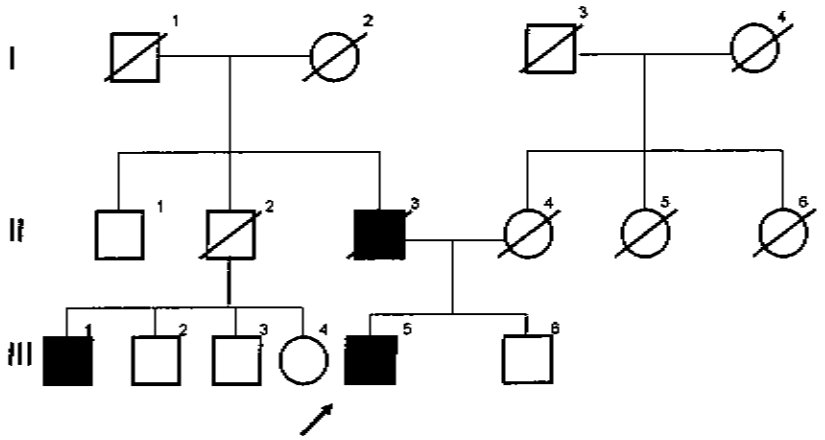


Figure 3.3 Family pedigree 3: High risk- Bethesda criteria positive

The paternal side of the proband's family in **Fig 3.3** is positive for the Bethesda criteria (**Table 1.5**- criteria no 3: Individuals with colorectal cancer and a first degree relative with colorectal cancer and/or an HNPCC extracolonic cancer and/or colorectal adenoma (cancer < 50 years and adenoma < 40 years)). Genetic testing is therefore indicated (MSI-testing). The proband's mother and her side of the family is not at increased risk for colorectal cancer above the general population.

3.5.4 Family pedigree-4 (High risk- Amsterdam criteria positive)

- **III-3**-Affected proband (arrow)- colorectal cancer diagnosed at age 39 years
- **II-4**-Father of proband - colorectal cancer diagnosed at age 40 years- died of colon cancer
- **II-2**-Paternal uncle of proband-colorectal cancer diagnosed at age 46 years
- **III-1**-Male first cousin of proband- colorectal cancer diagnosed at age 29 years
- I-1-Paternal great-aunt of proband - colorectal cancer diagnosed at age 35 years- died of colon cancer

None of the other relatives that died had cancer. The paternal side of the proband's family is positive for the Amsterdam criteria and genetic testing is indicated (mismatch repair gene testing)

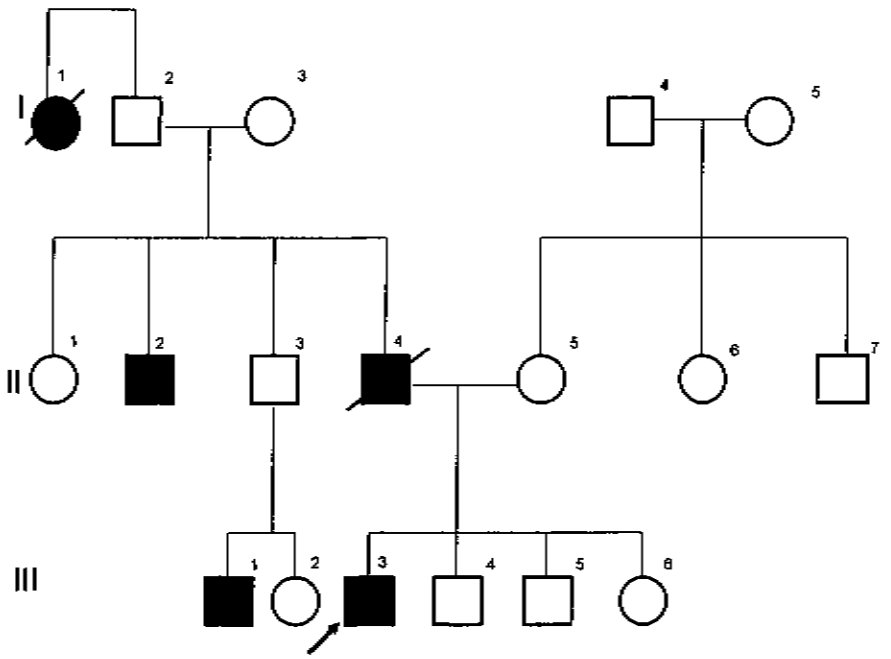


Figure 3.4 Family pedigree-4: High risk- Amsterdam criteria positive

3.6 Increase in patient numbers

A ten-fold increase in the number of patients counselled for inherited colorectal cancer was observed in the Division of Human Genetics (**Table 3.7**) as a result of follow-up on the research project questionnaire. The number of cases seen for inherited colorectal cancer over a similar time span (25 months) increased from 3 individuals/families (9% of cases) (data from departmental statistics) seen in the previous 25 months from May 2003 to May 2005 to 29 individuals/families (91% of cases) in the following 25 months (June 2005-June 2007).

Table 3.7 Increase in patient numbers

Colorectal cancer cases seen in 50 months- **Total**	**32**	**100%**
Cases seen in 25 months before institution of study	3	9%
Cases seen in 25 months after institution of study	29	91%

3.7 Patients' attitudes towards questionnaire, genetic testing and genetic counselling

General observations were made about the participants' attitudes and how they perceived the information sheet, the personal and family history questionnaire, the options for genetic testing

and the management issues that were discussed during the genetic counseling interview. The writer had the impression after counseling the participants that they were positive about receiving genetic counselling after completion of the questionnaire and that they were positive about the multidisciplinary service, the genetic testing and the sharing of their information with their relatives. None of the patients had genetic counselling prior to their genetic appointment. The two participants who were at moderate risk and were not offered further genetic testing, were also positive about the genetic counselling service and agreed to share the information with their relatives.

3.8 Patients' reasons for participation

Questions in the genetic counselling interview specifically about the inherited risk to affected study participant's children were very important to participants. One of the main reasons why patients with children wanted to take part in the cancer program and wanted to pursue genetic testing was to refine their childrens' risks. They were mostly concerned about the risks of colorectal cancer to future generations and thought that genetic testing and banking DNA would assist future generations in testing for inherited colorectal cancer and in preventing cancer. The patients also felt that other family members (siblings and parents) would benefit from genetic information and genetic testing.

Inherited risks to mostly first degree family members were therefore the main reason why patients already affected with colorectal cancer pursued genetic counselling and genetic testing. Overall, patients generally wanted genetic testing because they thought that it was important and they wanted to benefit from the international progress in the field of cancer

genetics. One patient was upset when he realized that South Africa's molecular diagnostic service for cancer genetics is inadequate and wondered why it was not already an essential service.

3.9 Concerns about confidentiality, discrimination and sharing of genetic information

In general, patients were not concerned about discrimination from medical aids or insurance companies because of genetic information and did not have any specific questions regarding the sharing of information with these third parties. All the patients seen requested that the writer send letters to their surgeons, oncologists and in some cases to their general practitioners to inform them about the surveillance and management protocols. It was the writer's impression that the patients generally demonstrated positive attitudes regarding the sharing of their genetic information with their general practitioners and specialists.

All the patients seen agreed that they would inform their relatives of their risks and the management of these risks. It was the writer's impression that they generally had positive attitudes regarding sharing the information with their extended families. Issues regarding confidentiality within families were addressed and none of the patients wanted to withhold genetic information from their relatives. It is uncertain whether all the interviewed patients (probands) informed their first-degree relatives about their increased cancer risks. This information is confidential and it would have been inappropriate to independently contact family members to ask them if they were informed of their genetic risks.

Only one family member has been in contact with the writer for a separate/individualized counselling session and this member also sent the writer a letter requesting that he wanted to be involved in any further research regarding colorectal cancer after his father died of his disease.

4. DISCUSSION

4.1 Primary observations

The self-administered questionnaire used in this cancer study provides a simple, reliable and acceptable way of collecting an unverified, but extensive personal and family history of cancer. The questionnaires need to be distributed by an interested and pro-active staff member for the program to work effectively and there may be difficulties in distributing the questionnaires to all the patients affected with colorectal cancer because of poor organization, rotating staff and lack of interest from health care professionals, especially in the state system. A self-administered, computerized tool for collecting a family history of cancer was validated in a previous study and the test-retest reliability was found to be high (Acheson, et al. 2006). The accuracy of a self-administered family cancer history questionnaire as a genetic counselling tool in a familial cancer setting at a familial breast and ovarian clinic in Toronto, Canada was also evaluated (McCuaig, et al. 2007). In this study the family history questionnaires were updated by asking targeted questions during a genetic counselling session. It was found that in only 15% of families (121 participants) the history required changes that led to a new risk assessment and that in only 5% of families changes altered the family's eligibility for genetic testing. Updating the questionnaire during a genetic counselling session therefore allowed for completion of the information obtained by the family history questionnaire and did not significantly alter genetic testing eligibility. This study concluded that the family history questionnaire is an effective tool and that it can also save approximately 20-30 minutes per counselling session.

The data from the completed questionnaire can therefore effectively be used to risk stratify families when decisions need to be made about who needs to be referred for a genetic assessment and genetic counselling. It is an easy entry point and fast assessment method for collecting information from individuals affected with colorectal cancer that is also useful in preparing for the genetic assessment and counselling session.

In the past referrals from other specialists and self-referrals from affected patients/families did not bring in the patient numbers that should have been seen at the genetic clinic for colorectal cancer. The risk assessment and screening criteria for inherited cancer are not easy to interpret and doing a full three generation family history on each patient during a normal non-genetic clinical consultation is too time consuming in any busy oncology, specialist or general practice clinic. Costs also escalate for each individual consultation if long periods are spent collecting extensive family history data, calculating genetic risks and addressing psychosocial issues related to inherited cancer, especially in private practice where the cost can double with a prolonged consultation. The large patient numbers that are seen daily, especially in medical oncology, makes it practically impossible for specialists to work out every individual's genetic risks and address psychosocial and ethical issues related to genetic testing.

Data used from the self-administered questionnaire to risk stratify families were reliable and correctly identified 97% of the increased risk families (medium and high risk) for inherited colorectal cancer. Only one patient was incorrectly classified and the risk classification decreased from medium to average risk in this family because the history of one of the relative's cancer was verified and was found to be prostate cancer rather than urinary tract/kidney cancer, which is an HNPCC-associated cancer. It was not possible to assess if

patients who were classified as average risk were truly at average risk because only increased risk (medium and high risk) patients were assessed clinically and had a formal pedigree study.

It was the writer's impression after counseling the moderate and high risk participants that they were positive about the clinical genetic service, the information sheet and method of collecting personal and family history data and the multidisciplinary approach related to the management of their inherited risks. Patients needed more information regarding management and surveillance for themselves and their family members' specific inherited risk. None of the patients had received any prior genetic counselling about the inheritance of colorectal cancer, the risks of cancer to family members and the psychosocial issues associated with this risk or the specific management guidelines for their risk. All the affected study participants from the high risk families were interested in genetic testing and in banking their DNA for future genetic work-up. The primary motivations for genetic testing included: wanting to know if more screening tests were needed, obtaining information about the risk for offspring, increasing certainty around their own risk and thinking that relatives could benefit from being informed of genetic risk. This corresponded to previous studies in the literature (Esplen, Madlensky, Butler et al. 2001) (Kohut, Manno, Gallinger, et al. 2007). The participants also demonstrated positive attitudes regarding the sharing of their genetic information with their general practitioners and specialists as shown previously by Esplen et al. (2001). Kohut et al. (2007) also demonstrated that patients affected with colorectal cancer understand that relatives could benefit from being informed of their genetic risk.

4.2 Patient numbers and risk stratification

A higher number of patients than expected (20%) (Lynch, et al 2003) were found to be in the increased risk category (moderate and high risk) (69%) compared to the average risk category (31%). There is also an unexpectedly high number of the increased risk category that were found to be at high risk (26 patients/93%) compared to moderate risk (2 patients/7%) after the clinical assessment and formal pedigree study.

Numbers were much higher in the high risk group than would be expected for inherited colorectal cancer in the general population (approximately 10%) (Lynch, et al. 2003) possibly because of selection bias. Selection bias may have existed if some specialists only referred or handed questionnaires to patients whom they thought were at sufficiently increased risk. It is also possible that only individuals who were concerned about their genetic risks because of their young age or significant family history decided to take part in the study. (see Limitations-**section 4.9.1**).

It is not possible to extract from these numbers the potential size of the affected colorectal cancer population in South Africa that needs clinical genetic assessment and counselling, as it may appear falsely high. It is also not possible to use these figures to extrapolate how many affected colorectal cancer patients/families in South Africa are eligible for mismatch repair gene testing. These numbers need to be extrapolated from international statistics or more comprehensive South African studies.

Colorectal statistics in the United States of America show that up to 20% of patients with colorectal cancer have increased risk (two or more first/second degree relatives (or both) with colorectal cancer) and that 5-10% of the total annual burden of colorectal cancer is Mendelian in nature (Lynch, et al. 2003). In the United Kingdom it is estimated that genetic factors may have a role in up to 30% of cases, but only a small proportion (up to 5%) arise in families with strong histories in which tumours develop at a young age (less than 50 years) and this represents truly high risk inherited predispositions. (Lynch, et al. 2003).

We can therefore estimate from these figures that approximately 20% of the yearly burden of colorectal cancer patients in South Africa will need genetic counselling and approximately 5% will need genetic testing and screening. This amounts to approximately 200 families per year in South Africa if only the reported cases are taken into account from the South African Cancer Registry (Mqoqi, et al. 2004). This number is conservative and may be higher if all colorectal cancer cases are reported in South Africa; all patients younger than 50 years are seen and if patients with families with other associated extracolonic cancers (HNPCC-associated cancers) are included. If the numbers from the research report were used, a figure of up to 700 families per year in South Africa that need genetic counselling would have been estimated if the limitations were not taken into account, as more than 2/3 of colorectal cancer cases evaluated (69%) were found to be at increased risk.

4.3 Patients' reasons for participation

Patients' participated because of concerns around inherited risks to first degree relatives, especially the genetic risks to their children. Most participants thought that genetic testing and

banking DNA would assist future generations in testing for inherited colorectal cancer and in preventing cancer. Participants also generally wanted genetic testing because they wanted to benefit from the international progress in the field of cancer genetics. The reasons for participation corresponded to previous studies in the literature which showed that the primary motivations for genetic testing included: wanting to know if more screening tests were needed, obtaining information about the risk for offspring, increasing certainty around their own risk and thinking that relatives could benefit from being informed of genetic risk (Esplen, Madlensky, Butler et al. 2001) (Kohut, Manno, Gallinger, et al. 2007).

4.4 Concerns about confidentiality, discrimination and sharing of genetic information

It was the writer's impression that patients were generally not concerned about discrimination from medical aids or insurance companies because of genetic information and that they did not have any specific questions regarding the sharing of information with these third parties. A previous study showed that barriers to genetic testing for colon cancer susceptibility included concerns about insurance, test accuracy and how one's family would react emotionally (Lerman, Marshall, Audrain, et al. 1998). Study participants in the current research project were however informed that their genetic risk information would remain confidential and would not be shared with any third parties (insurance companies and medical aids) unless they specifically gave written consent to share the information. They were also informed that it was their choice whether they wanted to share genetic information with a third party or not, as they were under no obligation to do so. As this area is still new in South Africa, guidelines need to be in place regarding sharing of cancer genetic information with third parties and discrimination before a comprehensive large scale inherited cancer program can be instituted.

These ethical guidelines are already in place in most European countries, the United States of America, Canada and Australasia (www.ornl.gov/hgmis/elsi/elsi.html). A survey of patient's experiences with the cancer genetic counselling process in various cancer genetics programs in the United States showed that only 5 out of 156 patients (3%) perceived, whether real or not, some form of insurance discrimination and that none of the participants experienced employment discrimination. However, misperceptions still exist in the USA regarding insurance discrimination and lack of insurance coverage for clinical cancer genetic services and cancer genetic testing. Insufficient coverage of testing by insurance companies and potential for insurance/employment discrimination were two reasons given by responders in this survey for not pursuing genetic testing (Kausmeyer, et al. 2006). In the USA, the Health Insurance Portability and Accountability Act (HIPAA) and the Americans with Disabilities Act (ADA) provide some protection on a Federal level and a number of states have enacted legislation to provide protection to its constituents (National Conference of State Legislatures/ www.ncsl.org/programs/health/genetics/ndishlth.htm) (Kausmeyer, et al. 2006). The Genetic Information Non- Discrimination Act from the National Human Genome Research Institute (NIH) also provides protection against genetic discrimination (www.genome.gov/10002077).

All the patients seen requested that the writer send letters to their surgeons, oncologists and in some cases to their general practitioners to inform them about the surveillance and management protocols. The participants demonstrated positive attitudes regarding the sharing of their genetic information with their general practitioners and specialists. This is in accordance with the literature, showing that most individuals would inform their attending physician about their genetic risks (Esplen, et al. 2001). The fact that the patients with an inherited risk did not have any objections to being managed by a team of professionals also

demonstrates their positive attitudes towards a multidisciplinary service and sharing of genetic information with other professionals involved in their management.

All the patients seen confirmed that they would inform their relatives of their risks and the management of these risks and they had positive attitudes regarding sharing the information with their extended families. Issues regarding confidentiality within families were addressed and it was the writer's impression that none of the patients wanted to withhold genetic information from their relatives. It is however uncertain whether all the interviewed patients (probands) informed their first-degree relatives about their increased cancer risks. This information is confidential and it would have been inappropriate to independently contact family members. A previous study showed that patients undergoing genetic testing for HNPCC generally understand that relatives could benefit from being informed of their genetic risk, but that they may not be willing or be able to inform all their family members. Patients should be engaged in a discussion on familial implications before genetic testing is done and an agreement can be formulated between the genetic counsellor and the patient regarding which of the relatives should be informed (Kohut, et al. 2007). A survey of patient's experiences with the cancer genetic counselling process in various cancer genetics programs in the United States showed that an overwhelming majority of patients (153 of 156 surveyed) (98,7%) shared information from their cancer risk assessment or genetic testing with family members. Means of communication with family members were in person (86.9%) and by telephone (69.3%). Less frequent means of communication included email (16.3%) and by letter (9.2%). The family tree was shared by 39% and 33.1% shared the summary/information letter. Only 15% of responders in this survey experienced difficulties or challenges with sharing genetic information with family members (Kausmeyer, et al. 2006).

The writer provided information sheets (cascade letters) (**Appendix 5**) with the genetic counselling letter to patients to hand out to their family members who may be at increased risk for cancer. The writer stated in this letter that family members could contact the Genetic Counselling Clinic staff should they need genetic counselling. Some patients asked that the writer send multiple copies of the cascade letters to them in order for them to hand the letters out to all their family members. However, only one family member has been in contact with the Genetic Counselling Clinic staff for a separate/individualized counselling session and this member also sent the Genetic Counselling Clinic staff a letter requesting that he wanted to be involved in any further research regarding colorectal cancer after his father died of his disease. The option of a separate counselling session for family members was stated on the final letter sent to the study participants. The relative short time available to evaluate this may be one of the reasons why the Genetic Counselling Clinic staff has not yet had any contact from other family members. Family members come for genetic counselling when the timing is appropriate for them.

4.5 Patients' needs and follow-up

Psychosocial issues and effects of treatment and diet were also discussed during the counselling sessions, as most of this information was not given to them by their treating specialists. Risk management programs were explained and stipulated in detail in the information letters sent. The patients counselled were also given the opportunity to phone us for a follow-up appointment if they felt there was a need or if they did not understand any of the information. None of the patients phoned us back for clarification of the information

shared after genetic counselling or for a follow-up appointment up to the time of submission of this research report. However, this was a relatively short time period to fully assess this need.

4.6 Advantage of the use of a printed self-administered questionnaire, information sheet and consent form

The printed personal and family history questionnaire with information sheet demonstrated an advantage over a computer based program in that it gave patients the opportunity to take the data collection sheet home to verify cancer histories, especially in second degree relatives. It has been shown at a clinical genetic centre in the United Kingdom (West Midlands Family Cancer Strategy, Clinical Genetics Unit, Birmingham Woman's Hospital) that completion of a family history data form in the patient's own time, at home, facilitates discussion with relatives to clarify relevant cancer history information and this method has saved time at primary care level when a cancer genetic referral was required (Cole, et al. 2000). Patients prefer to know prior to genetic counselling exactly what details of their family history are needed. Patients also understand that accurate information is important for the risk assessments.

If family history information is complete prior to the genetic appointment, time is saved during the genetic counseling session. It allows for construction of a family pedigree and for an initial risk assessment prior to the genetic counselling session. It also gives the health professional an opportunity to trace relevant and important pathological information prior to the genetic counselling session. Confirming tumour pathology with the pathology laboratory

involved in affected individuals and getting copies of their histopathology reports is an important step in the preliminary work-up of patients before they are seen for a formal genetic counselling session.

The self-administered questionnaire and information sheet should also be seen as an entry point to genetic counselling. It was developed to create a fast track service for cancer genetic referrals and should not be seen as removing medical practitioner authority in the decision process. Some specialists preferred referring the patients to us if they thought they were at sufficient inherited risk so that we could send the patients the questionnaires. It was not our intention to remove medical practitioner authority and this is now stated on separate information sheets drawn up specifically for the clinicians and their health care workers for the inherited cancer program that was developed after the end of this research project (**Appendix-7- Information sheet for doctors**). Educating clinicians on how the program works through these separate doctor information sheets may improve the use of the questionnaires. Clinicians are given the option of completing the questionnaires with their patients or of handing the questionnaires to their patients to complete. Patients are then advised by their doctors to take the questionnaires home if they need to verify family history information. Making the questionnaires part of the assessment of patients with cancer by giving the referring clinicians the option of completing and assessing information on the questionnaire may help in prompting some clinicians to use the questionnaires.

The questionnaire was patient based and the information sheets were specifically directed at patients. Patients needed to sign informed consent for us to have access to their medical files and histopathology reports. Patients/families that were at increased risk and excluded from

screening could not be identified if they were not handed the questionnaires. It remained the responsibility of the specialists or their health care workers and/or secretaries at the practices/clinics to hand out the questionnaires to the patients.

It is important that the questionnaires are given to all patients with colorectal cancer so that all patients can have a formal risk assessment, otherwise at risk patients and families may be missed. Feedback to treating specialists is important and should always be provided.

4.7 Increase in cancer genetic service awareness

As a result of this study, awareness of the availability and need for clinical genetic services for inherited colorectal cancer increased in the specialist practices used for the patient recruitment, as patients/families at risk for some of the other inherited cancer syndromes (e.g. breast/ovarian cancer syndrome) were also referred from these practices. Only a limited number of private practices and clinics participated in this research project. Cancer genetic referrals will increase, especially if more practices and hospitals are involved in patient risk assessment through the institution of a large scale program.

Awareness of how patients and families who are at risk of an inherited cancer syndrome ought to be managed and the importance of multidisciplinary involvement in the care of these individuals and families are essential components of basic patient care and management. Education is needed to increase this awareness. Patients should be informed that genetic counselling services are available and everyone should have access to these services. Litigation cases have been seen in other countries where there was a lack of careful

information sharing regarding inherited risks of cancer (Severin, 1996). This can be prevented if a large scale inherited cancer risk-assessment program is established through the self-administered questionnaires and information sheets. It will also prevent a situation where high risk cancer syndromes are under-diagnosed, incorrectly managed and not referred to genetic services. This program made the referral and assessment process for inherited colorectal cancer faster and easier and demonstrated that awareness can be increased if professionals and patients are actively involved in the process.

The field of cancer genetics is relatively young and many medical personnel, especially in South Africa with its limited resources, do not yet see it as an essential part of the care of individuals at risk for an inherited malignancy. The question of cancer inheritance was on the minds of all the patients seen, especially in patients that were young, who had other family members affected with cancer and in those who had children. Patients needed detailed information regarding the familial risks. Health professionals therefore need more education regarding the role of clinical cancer genetics in the overall management of patients at risk for inherited cancer. Motivated and pro-active doctors and medical personnel are needed who are positive about involving cancer genetics services in their practices. It is time consuming to draw a detailed three generation family tree, to inform patients about their risks of developing more or associated tumours and about the risk of cancer to their family members, to explain the clinical surveillance and management programs, the genetic basis of their cancer and the risk of recurrence in their children and to address the psychosocial issues. All these points are difficult to deal with during normal medical appointments and during busy oncology and specialist clinics where the primary focus is treatment and management of the cancer of the affected individuals. One or two separate appointments with a genetics professional, possibly

in a different environment, are therefore necessary and essential to address these issues and to direct genetic investigations.

Doctors need to become aware that they cannot deal with all these issues themselves and that cancer genetic services are essential in the comprehensive care and management of their patients. Establishment of a functional multidisciplinary service that involves all the necessary specialists is important in the management of inherited cancer, as demonstrated in this study. It is therefore necessary that information sheets are available that inform health care professionals why involvement of cancer genetic services is important. These information sheets have been drawn up as a result of this research project (**Appendix 7**- Information sheet for doctors).

Cancer genetics will also become more important as awareness of the inherited cancers increases in the public domain. Easy access of cancer information via the internet exists and this will also increase patient awareness of how inherited cancer should be managed. This will increase the patient numbers, as more patients will be empowered to personally contact clinical cancer genetic services.

4.8 Need for increased molecular diagnostic services

The study also highlights the urgent need to establish a cancer genetic diagnostic service in Johannesburg, not only for inherited colorectal cancer, but also for some of the other common inherited cancer syndromes, such as the breast/ovarian cancer syndrome.

4.9 Limitations of the study

4.9.1 Selection bias

Selection bias almost certainly existed in this study, as the writer had to depend on the specialists at most of the practices used in the study to hand out the questionnaires to the patients. It seems that some of the specialists only referred patients or handed questionnaires to patients whom they thought were at sufficiently increased risk. It appears as if treating specialists wanted to keep their autonomy in deciding who they wanted to refer. The questionnaires were therefore not handed to all the patients with colorectal cancer at most of the practices/clinics used for patient recruitment. It is uncertain what criteria were used to determine who at the end received the questionnaires.

In one of the oncology practices patients were not selected by their specialists to participate in the program as questionnaires were handed out to the patients by an unbiased pro-active non-medical staff member before or after their oncologist saw them. Sixty- five percent (65%) (31/48) of the patients recruited for this study came from this practice and 14/15 families (93%) who were found to be at average risk completed their family history questionnaires at this practice. Increased risk patients were found to be 55% of the total from this practice and the average risk patients were 45% of the total number of patients from this practice. These numbers are closer to the numbers that are expected in the average population (section 4.2), indicating that some selection bias was removed if staff members not directly involved in patient management handed out the questionnaires. A primary link with a motivated, interested and pro-active staff member therefore played an essential role in recruiting patients

at this practice as the numbers were much higher of average risk patients compared to the other practices where increased risk patients were selected by specialists for participation in the program.

Patients who contacted us or who were referred to our department and subsequently sent questionnaires were also selected either by their referring specialists or by their own knowledge of their strong colorectal cancer family histories.

Patients who took part in the research at all the recruitment sites may have contributed to the selection bias, as it is possible that only individuals who were concerned about their genetic risks because of their young age or family histories decided to take part in the study and complete the self-administered questionnaire, even after it was handed to them. Patients had a choice if they wanted to take part in the program after they read the information sheet and it was not possible to remove this bias.

Selection bias may also have existed in observations regarding the numbers of patients who had a positive response to the program and the genetic counselling service. Patients and family members who completed the self-administered questionnaire were already more interested in their risks, were motivated to receive genetic counselling and wanted to participate in the research. This may be a reason why the writer had the impression that all the patients/families seen were positive about the service. Patients who did not complete the questionnaires were not ascertained in any way.

Ascertainment bias also existed because the questionnaire was aimed at individuals affected with colorectal cancer and was only used at tertiary/ specialist level where a diagnosis of colorectal cancer already existed in the proband. Patients/families would have been missed with the questionnaire used if they presented with any other cancer, for example endometrial cancer, upper gastrointestinal cancer, cancer of the biliary tree or renal/renal tract cancer, which are all HNPCC-associated cancers. The questionnaire was also not able to identify patients/families where there was only a history of pre-malignant colonic polyps. Patients affected with polyps are usually not referred to oncologists (mainly oncology practices were used). However, a family history of colonic polyps was listed by some patients and was assessed during the clinical genetic assessment in all the medium and high risk families.

4.9.2 Limited population representation

The study is not representative of the South African patient population. A well-educated urban and suburban population seen at a tertiary/ specialist level was used. All the patients who filled in questionnaires were able to understand and speak English and none of the patients who filled in the questionnaire needed a translator. The two black patients that participated in the study were fully multilingual and the two Indian and two coloured patients that participated were English speaking.

More patients with European ancestry (42 patients) participated in the study because the patient populations from the private practices consisted mostly of this population group. The ascertainment was poor in the state sector, as only five patients participated in the study. It would appear as if questionnaires were not often handed to patients in the state hospitals and

clinics because questionnaires were left at a certain place in the ward or clinic and the same number of blank questionnaires would remain in the ward or clinic month after month. It may be a function of the changing rotations of the medical personnel and the lack of communication between the medical personnel when they move to other sections/specialties. More education is needed at the state hospitals and this will be a major point to be addressed when starting a comprehensive inherited cancer program. It will also be preferable to make the questionnaires available in two or three common African languages, as well as in English and Afrikaans when establishing a large-scale program.

The patients recruited for the study are therefore not a direct representation of the patient population in South Africa. From this study, it is not possible to compare and assess the effectiveness, acceptance and applicability of program in all the different population groups and sectors of our society in some of which knowledge of family medical history may be poorer. The study can also not highlight the problems expected in our multilingual and varied society with its rural, suburban and urban community.

4.9.3 Validity of family history questionnaire

This study was not aimed at validating the family history questionnaire by comparing patient self-reported data with cancer registries and genealogical data. The validity of the questionnaire used is limited in the South African context, as only European, American and Canadian centres (Mussio, et al. 1998) (McCuaig, et al. 2007) have validated similar family history questionnaires in their populations. Cancer registries and genealogical data were used to assess the accuracy of patient self-reported data by Mussio, et al. (1998). The accuracy of a

self-administered family cancer history questionnaire as a genetic counselling tool in a familial cancer setting at a familial breast and ovarian clinic in Toronto, Canada was evaluated by McCuaig, et al. (2007) and in their study the family history questionnaires were updated by asking targeted questions during a genetic counselling session. However, an attempt was made by the writer in this research project to verify personal and family history data by comparing information in the completed questionnaires with information gained personally from the study participants during the clinical genetic assessment in the moderate and high risk participant groups.

Traditional family views of cancer and how it is perceived in the African culture may influence the accuracy of self-reported family histories in our population. The question of accuracy of patient self reported data in the South African context therefore remains largely unresolved.

4.9.4 Limited patient numbers

Numbers are small because of the prospective nature of the study and the poor cooperation of some of the clinicians. Only patients that were newly seen or followed-up for colorectal cancer at the specialist clinics were recruited. We did not retrospectively look at any patient records and did not contact any patients that were previously seen for colorectal cancer at these practices because of the confidential nature of their personal and cancer information. Patients enrolled in this study had to sign consent before we could have access to their medical files and/or histopathology reports. The time span (approximately 2 years) set up for recruiting patients for the research project also limited the numbers.

4.10 Uniqueness of the study

This study is unique in that it is the first time that a step-wise program using a self-administered questionnaire and information sheet for an inherited cancer syndrome has been developed in South Africa. No similar study exists in the South African medical literature. It is also the first time that surveillance and follow-up genetic counselling services for inherited colorectal cancer were formally instituted in Johannesburg with a view to creating a multidisciplinary team approach in the management of colorectal cancer.

Another unique feature of the study was that it not only addressed the effectiveness of using patient and family history information in risk estimation, but also anecdotally assessed the attitudes and feelings of patients regarding genetic testing, genetic counselling, sharing of genetic risk information and the multidisciplinary management of their inherited cancer risks.

The unique observations from this study have been used in the planning and setting up of a new inherited cancer program for all the inherited cancer syndromes for our patient population in the Clinical Section of the Division of Human Genetics, National Health Laboratory Service and the University of the Witwatersrand (section 4.11- future directions). This was mainly achieved by drawing up a new personal and family history information questionnaire, a new patient information sheet and a doctor information sheet (**Appendix 7**).

This study is further unique in that it helped to create awareness of the importance of genetic counselling and testing in inherited cancer management at the practices/clinics used for the

recruitment of the study participants. It is important that this information is brought to a wider group of practices where patients with cancer are managed.

This study is the first of its kind that formally highlights the urgent need for a molecular genetic diagnostic service for inherited colorectal cancer in Johannesburg, as many patients in this study were found to be at high risk and they needed histopathological as well as genetic testing for the work-up and confirmation of their diagnosis and for subsequent cascade testing of family members. It also highlights the urgent need for cancer molecular diagnostic services for all the other inherited cancer syndromes. It is hoped that this need will be addressed and that diagnostic services will be instituted.

4.11 Future directions

This study formed a platform from which further planning was done to develop a comprehensive family program for all the inherited cancer syndromes (**Appendix 6, Appendix 7**). This new family cancer program was introduced into the Clinical Section at the Division of Human Genetics, National Health Laboratory Service and the University of the Witwatersrand in July 2007. It consists of a new personal and family history questionnaire, a new patient information sheet and a doctor information sheet. The new and concise personal and family history questionnaire developed was not only based on the findings regarding the limitations of the questionnaire used in this research project, but also on previous family cancer questionnaires developed in the UK and Canada, i.e. the West Midlands Family Cancer Strategy, UK (Cole, et al. 2000) and the Familial Breast and Ovarian Clinic Family History Questionnaires of Princess Margaret Hospital, Toronto (McCuaig, et al. 2007). The new

program includes cancers of all types and sites as well as the phenotypic manifestations of all the inherited cancer syndromes. This will be beneficial for the management, counselling and genetic testing of patients and families at risk for any of the inherited cancer syndromes. It will also help in the establishment of clinical cancer genetics as an essential component of care of patients and families affected with cancer.

This new step-wise family cancer program is also aimed at contributing to a more effective cancer genetic service in Johannesburg. The new questionnaires are being sent to all new patients referred to our Clinical Division for inherited cancer. It is currently working well and patients appear to find it easy to complete and return to the genetic counseling clinic. It helps in planning genetic counselling sessions by preliminary pedigree construction, risk estimation and in collecting important histopathological and family data. The new program can in future be distributed to practices and clinics in Johannesburg where patients with cancer are managed. It can later be expanded to population level and can be made available in all the different languages in South Africa.

Many of the limitations of this study discussed in section 4.9 can also be reduced by the new questionnaire, because it includes questions on the various phenotypic manifestations of the inherited cancer syndromes (i.e. colonic polyps, skin tumours) and it is directed at all cancers, decreasing ascertainment bias. Implementing the program at primary and secondary care level will also help in making it more comprehensive for the whole patient population and more sensitive in identifying families where members present with a premalignant condition or with an associated cancer, like in HNPCC. However, awareness of inherited cancer is needed at all levels of care for the successful implementation of a comprehensive program in South Africa.

The success of such a program relies on the co-operation of clinicians making diagnoses and managing patients with cancer.

Studies on the accuracy of the family history questionnaire in our population should be done in future. The questionnaire's accuracy at collecting personal and family cancer history information in the South Africa context should therefore be validated. The population differences in family cancer history reporting, how cancer is perceived in the different population groups and how this will influence risk calculations will help in validating the questionnaire. Studies on the psychological impact of inherited cancer in the different population groups of South Africa and how information sharing with relatives varies in different cultures in South Africa are also needed in future research on this topic.

Studying the molecular nature of the different cancer syndromes in the South African context is essential because of population differences in mutations and because of the potential role of founder effects (Weber, Chin, Rodriguez-Bigas, et al. 1999). Population differences in inherited cancer statistics may also exist and this needs to be studied. It is now the appropriate time to set up a comprehensive family cancer program and inherited cancer registry for South Africa. Many issues related to molecular cancer diagnostics are unresolved in the South African context and there is enormous potential for molecular research in this field. Genetic counselling professionals also have to increase cancer genetic referrals to clinical genetic divisions across South Africa. Patient numbers need to increase for the institution of diagnostic cancer genetic services and to do the much needed molecular research.

The molecular data from this research report will be entered into an inherited cancer registry database at the Clinical Division of Human Genetics, National Health Laboratory Service and University of the Witwatersrand, once the confirmatory genetic testing is completed. This will be completed as a first attempt at the subsequent identification of population differences in genetic mutations for inherited colorectal cancer that may be present in the South African context.

More African patients need to be recruited for future research on this topic because novel *hMLH1* and *hMSH2* germ line mutations have been identified in African-Americans with colorectal cancer (Weber, Chin, Rodriguez-Bigas, et al. 1999). It would therefore be interesting to see if these mutations for HNPCC also occur in the local African population. The newly developed family cancer program will be instituted at more levels of care and it is hoped that there will be an increase in patient numbers from all the different population groups in South Africa.

In future research, patients and families from different population groups with a confirmed inherited cancer syndrome/positive genetic test result can also be followed up to observe if phenotypic differences are present in the malignant behavior of the inherited tumours in the different population groups. This can be done once an inherited cancer registry is established.

Future research, patient recruitment and data collection for all the inherited cancer syndromes can therefore be done based on experience gained through this study.

5. SUMMARY AND CONCLUSIONS

The information sheets and self-administered patient-based questionnaires provided a reliable and acceptable way of collecting unverified personal and family histories of cancer. The histories were extensive and adequate for risk stratification of families for inherited colorectal cancer. Personal histories that were provided on the questionnaires were generally accurate and family histories provided were accurate in more than 95% of the increased risk patients seen. The questionnaires used in this study were easy to interpret and collected information in an efficient and confidential manner that was essential in the further planning of the cancer genetic counselling process. It made it easier for health care professionals dealing with individuals and families affected with colorectal cancer to refer patients to genetic counselling and testing services and for them to be managed in the genetic counselling service. Opportunities to prevent inherited colorectal cancer in first and second degree relatives will be less likely to be missed if the program can be instituted on a large scale. It will also eventually lead to a large increase of referrals and a decrease of inappropriate referrals to cancer genetic counselling and testing services.

Patients were effectively recruited and patient referrals for inherited colorectal cancer increased by more than 80% to the Clinical Genetics Section, Division of Human Genetics, National Health Laboratory Service and University of the Witwatersrand. Awareness of cancer genetic services was improved at the practices/clinics involved in this study. This awareness need to be expanded to other practices/clinics in Johannesburg and to more levels of care.

Staff cooperation and motivation to hand out the questionnaires to patients at the clinics were essential to the success of the study. However, there is always the potential for patients not to complete the questionnaires and it may be expected that younger patients and those with more significant family histories will be more proactive.

All the participants counselled appeared to be positive about the clinical genetic counselling and testing service and about the multidisciplinary management of their and their families' inherited risks. High risk colorectal cancer patients were all interested in further molecular work-up. This highlighted the urgent need to expand molecular genetic diagnostic services for inherited cancer.

This study formed the basis from which a new family cancer program, extended to all familial cancers, was developed with a doctor information sheet, a new and more generalized personal and family history questionnaire and a new patient information sheet. This new family cancer program was developed to reduce some of the limitations (section 4.9) identified with the questionnaire used in this research project. The new program was introduced into our Clinical Genetic Section of the Division of Human Genetics, National Health Laboratory Service and University of the Witwatersrand in July 2007 and is used as a data collection tool for all the inherited cancer syndromes, including colorectal cancer. An inherited cancer registry will be started from the clinical and molecular data obtained during this research project (but not presented in this report) and from future molecular data of newly recruited patients. Information in this registry will be an invaluable data source for future inherited cancer genetic research in South Africa.

Clinicians, medical administrative personnel, nursing staff and patients will eventually become more aware of the availability of cancer genetic counselling and testing services. This will especially be seen once the new family cancer program is instituted on a large scale, information sheets for doctors and medical personnel are widely distributed and more education is done at all levels of care. Referrals from doctors and other health care professionals as well as self-referrals are then expected to increase. This will lead to the expansion of cancer genetic counselling services, cancer molecular diagnostic testing services and of research related to inherited cancer in South Africa.

APPENDIX 1

FDR – first degree relative, SDR- second degree relative

STEP 1 – Initial screening questionnaire and consent form **(Appendix 2 and 3)**

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STEP 2 – Classify patients into three risk groups according to validated criteria.
Less restrictive criteria than the Amsterdam II criteria are used because the Amsterdam criteria are not intended to serve as a guide to exclude families from cancer genetics consultation or mutation analysis. The criteria are more inclusive and sensitve than the Amsterdam II criteria (Hampel et al. 2004).
e.g.

COLON:
High risk hereditary non-polyposis colon cancer (HNPCC):
Any of the following:
-3 FDRs or SDRs affected with any HNPCC associated cancers; all cases can occur in one generation, no age restriction.
HNPCC associated cancers include colorectal, endometrial, stomach, ovary, small bowel, pancreas, ureter, or renal pelvis cancer (as ureter and renal pelvis are too specialized to include on general screening questionnaires, "kidney" can be accepted in lieu of these subtypes.
-1 FDR or SDR with two or more HNPCC associated cancers
-1 FDR with colorectal carcinoma < 50 years (this will confer high risk to FDRs of the index case if the index case is < 50 years)

Moderate risk colon:
1 FDR with colorectal carcinoma ≥ 50 years and 1 SDR with colorectal carcinoma at any age
2 FDRs with colorectal carcinoma ≥ 50 years

Polyposis : (High risk)
Any FDR or SDR with > 10 polyps

Rare cancer syndromes: (High risk)
Two family members have related rare cancers or two family members have the same rare cancer
Rare extracolonic cancers present, i.e. medulloblastomas in Turcot syndrome
Cancer diagnosed 5-10 years earlier than what is usual for the specific type of cancer
Specific non-malignant extracolonic manifestations present that are associated with a rare cancer syndrome

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STEP 3 - Risk notification and recommended cancer genetic consultation depending on risk

APPENDIX 2

On the following pages are included the information sheet, consent form and assent form used in this study:

2a) Information sheet and consent form for patients

2b) Information sheet and consent form for parents (in case of minors <18 years old)

2c) Assent form (for minors< 18 years old)

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Consent form and information sheet

Dear patient

My name is Dr Andre van der Westhuizen and I am from the Department of Medical Genetics, University of the Witwatersrand and National Health Laboratory Service (NHLS). We would like you to take part in a study to establish a method to identify individuals and/or families at risk for inheriting colorectal cancer (cancer of the large bowel). We are developing a screening program to make referrals to our Genetic Counselling Clinic more effective.

Our aim is to identify if there is a possible familial risk in your type of cancer. We want to identify and help patients and their families who have colorectal cancer or are at risk for developing it because of a familial or inherited predisposition. We are also starting a multidisciplinary service where patients and/or families will be counselled regarding their familial risks, genetically tested if appropriate and managed according to international standardised protocols. The management will mainly focus on identifying patients and family members at an early stage who have inherited a colorectal cancer predisposing gene, in order to prevent serious disease and will be done in collaboration with your doctor.

In order for us to do this, we would like you to answer some questions about your illness and about your family history. We have chosen colorectal cancer because sometimes it may be inherited. We are asking you to spend approximately 10 to 15 minutes to complete the questionnaire attached. You may take the questionnaire home if you cannot remember all the information that is being requested. You can bring the completed questionnaire back to the hospital/clinic/practice or you can fax it to us at 011 489-9226 (Attention- Dr A vd Westhuizen). You can also phone me (numbers are provided below) if you need me to arrange collection of the questionnaire. We would also like to ask your permission for access to your medical records because we need specific information regarding the histology (microscopic appearance) of your cancer.

It is important to note that all information will be treated with the greatest confidentiality (no one else will be allowed to see your information). You may refuse to answer some of the questions if you choose. If you decline to participate or if you decline to answer some questions, you can be certain that it will not affect your treatment by your specialist in any way. You are also free to withdraw from the study at any time.

If, after completing this questionnaire and after assessment by me, we feel that you may be at increased risk for inherited colorectal cancer, you will be contacted telephonically and genetic counselling by a genetic professional will be arranged at a time convenient to you. This will be done in order that you and your family understand fully the potential risks involved and options available in dealing with these risks.

This is a consent form. Please sign and date it here to show that you have understood what has been written (or said to you by an interpreter) and that you willingly agree to answer questions and that you give us permission to use your medical records.

Signature _____ Date:_____
Name : _____
Signature of witness (in case of verbal consent)_____
Date:_____

If you need interpretation of the questionnaire or need more information regarding the study, or if you wish to discuss some aspects of your cancer, please do not hesitate to contact me on the following numbers: 011 489-9902/ 082 605 1128/ 011-489-9224. I can arrange with someone at your specific clinic to help you with the interpretation of the questionnaire, should there be any difficulties in understanding English.

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Consent form and information sheet for parents

Dear parents

My name is Dr Andre van der Westhuizen and I am from the Department of Medical Genetics, University of the Witwatersrand and National Health Laboratory Service (NHLS). We would like your child to take part in a study to establish a method to identify individuals and/or families at risk for inheriting colorectal cancer (cancer of the large bowel). We are developing a screening program to make referrals to our Genetic Counselling Clinic more effective.

Our aim is to identify if there is a possible familial risk in your child's type of cancer. We want to identify and help patients and their families who have colorectal cancer or are at risk for developing it because of a familial or inherited predisposition. We are also starting a multidisciplinary service where parents, patients and/or families will be counselled regarding their familial risks. Individuals and their families will be genetically tested if appropriate and managed according to international standardised protocols. The management will mainly focus on identifying patients and family members at an early stage who have inherited a colorectal cancer predisposing gene, in order to prevent serious disease. This will be done in collaboration with your doctor.

In order for us to do this, we would like you to answer some questions about your child's illness and about your family history. We have chosen colorectal cancer because sometimes it may be inherited. We are asking you to spend approximately 10 to 15 minutes to complete the questionnaire attached. You may take the questionnaire home if you cannot remember all the information that is being requested. You can bring the completed questionnaire back to the hospital/clinic/practice or you can fax it to us at 011 489-9226 (Attention- Dr A vd Westhuizen). You can also phone me (numbers are provided below) if you need me to arrange collection of the questionnaire. We would also like to ask your permission for access to your child's medical records because we need specific information regarding the histology (microscopic appearance) of his/her cancer.

It is important to note that all information will be treated with the greatest confidentiality (no one else will be allowed to see the information). You may refuse to answer some of the questions if you choose. If you decline participation of your child or if you decline to

answer some questions, you can be certain that it will not affect the treatment by the specialist in any way. You are also free to withdraw your child from the study at any time.

If, after completing this questionnaire and after assessment by me, we feel that your child may be at increased risk for inherited colorectal cancer, you will be contacted telephonically and genetic counselling by a genetic professional will be arranged at a time convenient to you. This will be done in order that you and your family understand fully the potential risks involved and options available in dealing with these risks.

This is a consent form. Please sign and date it here to show that you have understood what has been written (or said to you by an interpreter) and that you willingly agree to answer questions and that you give us permission to use your child's medical records.

Signature _____ Date:_____
Name : _____
Signature of witness (in case of verbal consent)_____
Date:_____

If you need interpretation of the questionnaire or need more information regarding the study, or if you wish to discuss some aspects of your child's cancer, please do not hesitate to contact me on the following numbers: 011 489-9902/ 082 605 1128/ 011-489-9224. I can arrange with someone at your specific clinic to help you with the interpretation of the questionnaire, should there be any difficulties in understanding English.