AN INVESTIGATION INTO FACTORS WHICH HAVE AN IMPACT ON ACCESS TO AND UTILISATION OF THE GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC OFFERED TO HIGH-RISK MEMBERS OF KNOWN LYNCH FAMILIES.

ZANDRé BRUWER
BRWZAN001

Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

In the Division of Human Genetics

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

August 2011

Supervisor: Professor Rajkumar Ramesar

Co-supervisors: Dr Merle Futter

Professor Kruijsse

Division of Human Genetics
Department of Clinical Laboratory Medicine
University of Cape Town

DECLARATION

I, Zandré Bruwer, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Signature:……..

12 August 2011

ABSTRACT

BACKGROUND

The Genetic and Endoscopic Surveillance Clinic has been in operation for more than a decade and provides predictive testing and life-saving colorectal cancer screening services to individuals with Lynch syndrome, in the Western and Northern Cape provinces of South Africa. The risk of colorectal cancer is reduced by 50% and mortality is decreased by 65% with regular colonoscopic screening; however, the attendance rate at the clinic has been declining over several years. Obvious concerns exist for those individuals undergoing screening at levels below the desired recommendations in light of the recognised preventative benefits of frequent surveillance. It was thus opportune for a formal evaluation of both the surveillance and predictive testing programmes to be conducted to determine factors affecting the access, utilisation and satisfaction with the service, from the perspective of the service users.

AIMS

The aims of this study were:

- To appraise the clinic from the users' perspective using face-to-face interviews to ascertain their experiences and level of satisfaction with the surveillance and predictive testing aspects of the clinic;
- To measure the level of the adherence to recommended surveillance screening guidelines;
- To determine the impact of socio-economic status, education, physical barriers and psychosocial factors on adherence to the recommended surveillance programme;
- To determine the uptake of predictive testing among participants and their family members;
- To identify and explore the referral pathways and communication networks, leading to attendance at the clinic.

METHODOLOGY

The research used a phenomenological design with a 'multi-method' approach of both qualitative and quantitative methods. A semi-structured interview schedule, consisting of both open- and closed-ended questions, was developed and two cohorts were interviewed to evaluate the surveillance and the predictive testing programme offered through the Genetic and Endoscopic Surveillance Clinic.

The two groups comprised:

- **Group A.** A cross-sectional design was utilised to gather information from participants already involved in the screening programme for longer than one year (n=83).
- **Group B.** A longitudinal approach, consisting of three interviews, was used to collect data from individuals requesting predictive testing (n=33).

Audio-recordings were conducted for each interview, and the data was transcribed and captured on Excel spreadsheets. The quantitative data was analysed by Categorical Principle Component Analysis and qualitative data by means of a thematic analysis approach.

FINDINGS

The majority of participants within Group A were satisfied with the services offered by the clinic (90.2%). Although their average level of knowledge of Lynch syndrome was relatively poor, a higher knowledge score appeared to relate to a longer period within the programme. Participants who missed most of their colonoscopic appointments were generally female, over the age of 50 years, and needed to travel for longer than one hour on the free ambulance transportation service to get to the surveillance clinic. Rates of compliance to recommended colonoscopies differed when comparing figures obtained from self-report to that of calculated uptake rates. Fewer than a quarter of

participants were adherent with all their recommended screening appointments. The barriers to screening pertained mostly to colon preparation and transport concerns. Additional factors affecting compliance and unique to the clinic, were identified. Although participants disclosed their genetic test result to their immediate family members on the same day that they received the information, the implications and option of predictive testing were not always relayed immediately. The calculated uptake rate of predictive testing among siblings and eligible children was 97% and 73.6%, respectively. Under-exposure rather than over-exposure to the familial cancer was found to be an important predictor of psychological distress in individuals with Lynch syndrome.

The vast majority of participants in Group B judged the predictive testing programme as 'highly satisfactory' (80.3%) and had been referred to the clinic by a family member, usually a parent with Lynch syndrome. Regret of having undergone predictive testing for the familial susceptibility was not expressed and all participants stated that they would recommend testing to their family members. Of concern were the 39.4% of participants who could not explain the purpose of predictive testing following their pre-test counselling session. These individuals were mostly from a lower socio-economic and education background and of Mixed Ancestry. The uptake rate of predictive testing, however, remained high with a 100% of participants accepting testing and 70% presenting within a year of learning about the availability of a genetic test. The psychological impact of predictive testing, on anxiety and depression, was congruent with reported findings in the literature. However, cancer worry scores were unexpectedly higher among mutation-negative individuals when compared to the mutation-positive cohort.

CONCLUSION

Recommendations for improvements in both the surveillance and predictive testing services offered through the Genetic and Endoscopic Surveillance Clinic were made by the participants in Group A, Group B and the

researcher. The majority of these changes have been implemented, however, they will also require further evaluation after the improved services have been in operation for a period of one year.

ACKNOWLEDGEMENTS

My sincerest thanks to those that helped me complete this study. Your contribution, guidance and support during this time was invaluable:

- I owe a considerable debt to my supervisor and co-supervisor, Professor Raj Ramesar and Dr Merle Futter, who not only provided detailed comments on the entire manuscript but offered tremendous support, suggestions and constructive criticism throughout the study. The insight into both the clinical background and research methodology were invaluable.
- Professor Herman Kruijsse (PhD) for his statistical advice and assistance throughout the study.
- Ursula Algar for sharing her incredible knowledge and passion on Lynch syndrome, which has stemmed from many years of working closely with families affected by the condition. The unflinching support, determination and perseverance in contacting participants for the study was deeply appreciated.
- The participants who welcomed me into their homes and shared their experiences and personal details so readily and openly.
- Professor Jacquie Greenberg for her invaluable support, motivation and expertise in genetic counselling and for always having an open door policy for any enquiry.
- Latiefa Jattiem, Natalie Jacobs, staff, students and genetic counsellors in the Division of Human Genetics, who created such a supportive and pleasant working environment.
- Professor Paul Goldberg for allowing me to evaluate the Genetic and Endoscopic Surveillance Clinic.
- My parents, Marguerite and Justus, who may now perhaps regret stating that I could always study for as long as I wanted. I am eternally grateful for the continuous financial and emotional support throughout all the years of studying. My husband, Peter, for all his

unselfish sacrifice, motivation, patience, love and support during this time.

- The South African MRC for funding the research and attendance at one international and two national conferences.
- The Struwig-Germeshuysen Kankernavorsingstrust for their financial assistance.

TABLE OF CONTENTS

DECLARATION……i
ABSTRACT……ii
ACKNOWLEDGEMENTS……vi
TABLE OF CONTENTS……viii
LIST OF FIGURES, TABLES AND PHOTOGRAPHS……xii
LIST OF ABBREVIATIONS……xvii
GLOSSARY……xix
PREFACE……xxi

CHAPTER ONE (INTRODUCTION)……1
1.1 INTRODUCTION……2
1.2 SIGNIFICANCE OF THE STUDY……5
1.3 AIMS OF THE STUDY……6
1.4 OBJECTIVES OF THE STUDY……7
1.4.1 BACKGROUND INFORMATION……7
1.4.2 UNDERSTANDING, EXPERIENCE AND SATISFACTION WITH THE SERVICE DELIVERED……7
1.4.3 REFERRAL PATHWAYS AND COMMUNICATION NETWORKS LEADING TO ATTENDANCE AT THE SERVICE……8
1.4.4 IMPROVE SERVICE OFFERED TO PARTICIPANTS AND THEIR FAMILIES……8
1.5 OUTLINE OF RESEARCH DESIGN AND METHODOLOGY……9
1.6 ORGANISATION OF THE STUDY……9

CHAPTER TWO (LITERATURE REVIEW)……12
2.1 INTRODUCTION……13
2.2 COLORECTAL CANCER (CRC)……14
2.2.1 ETIOLOGY OF COLORECTAL CANCER……14
2.3 OVERVIEW OF LYNCH SYNDROME (LS)……16
2.4 MOLECULAR BASIS OF LYNCH SYNDROME……17
2.5 CLINICAL FEATURES OF LYNCH SYNDROME……18
2.5.1 GENDER DIFFERENCES……20
2.5.2 GENOTYPE-PHENOTYPE……20
2.5.3 HISTOPATHOLOGY……20
2.6 DIAGNOSTIC CRITERIA……21
2.6.1 AMSTERDAM CRITERIA……21
2.6.2 BETHESDA GUIDELINES……23
2.6.3 MICROSATELLITE INSTABILITY (MSI)……24
2.6.4 IMMUNOHISTOCHEMISTRY (IHC)……25
2.6.5 RISK ASSESSMENT MODELS……26
2.6.6 MOLECULAR TESTING……26
2.7 EPIDEMIOLOGY OF LYNCH SYNDROME……27
2.7.1 FOUNDER MUTATIONS……32
2.8 CANCER SPECTRUM AND SURVEILLANCE……33

2.8.1 COLORECTAL CANCER....34
2.8.2 ENDOMETRIAL CANCER....36
2.8.3 OVARIAN CANCER....37
2.8.4 BREAST CANCER....38
2.8.5 GASTRIC CANCER....39
2.8.6 SMALL BOWEL CANCER....40
2.8.7 PANCREATIC AND BILIARY CANCER....42
2.8.8 URINARY TRACT CANCER....43
2.8.9 BRAIN CANCER....44
2.8.10 SKIN CANCER....44
2.9 LYNCH SYNDROME – THE SOUTH AFRICAN CASE....48
2.9.1 MANAGEMENT OF LYNCH SYNDROME IN SOUTH AFRICA....48
2.10 PREDICTIVE TESTING FOR LYNCH SYNDROME....49
2.10.1 PREDICTIVE TESTING AND COUNSELLING PROTOCOL....50
2.10.2 PRE-TEST COUNSELLING....51
2.10.3 RISK PERCEPTION....52
2.10.4 INFORMED CONSENT....52
2.10.5 POST-TEST COUNSELLING....56
2.11 PSYCHOLOGICAL IMPACT OF GENETIC TESTING ON THE INDIVIDUAL....57
2.11.1 UPTAKE OF PREDICTIVE TESTING....60
2.11.2 BARRIERS AND FACILITATORS TO PREDICTIVE TESTING....61
2.11.3 BARRIERS AND FACILITATORS TO SURVEILLANCE....62
2.12 IMPACT OF LYNCH SYNDROME ON THE FAMILY....65
2.12.1 COMMUNICATION OF THE GENETIC INFORMATION TO THE FAMILY....65
2.12.2 ETHICAL ASPECTS: FAMILIAL NATURE OF LYNCH SYNDROME....68
2.13 GENETIC COUNSELLING....70
2.14 SATISFACTION WITH GENETIC COUNSELLING SERVICES....72
2.15 OVERVIEW OF SOUTH AFRICA: POPULATION AND HISTORY....75
2.15.1 PROFILES OF THE NORTHERN AND WESTERN CAPE COMMUNITIES....78
2.16 HEALTHCARE SYSTEM IN SOUTH AFRICA....79

CHAPTER THREE (METHODOLOGY)....82
3.1 INTRODUCTION....83
3.1.1 ANALYSIS OF EXISTING DATA PRIOR TO INTERVIEWING PARTICIPANTS....83
3.1.2 INTERVIEWS....84
3.1.3 RECOMMENDATIONS TO IMPROVE AND INCREASE UPTAKE OF THE SERVICE....84
3.2 RESEARCH DESIGN....84
3.3 PARTICIPANTS AND SETTING....87
3.3.1 SAMPLING-METHOD AND SELECTION....87
3.3.2 RESEARCH SETTING....91
3.4 ELIGIBILITY CRITERIA....91
3.4.1 INCLUSION CRITERIA....91
3.4.2 EXCLUSION CRITERIA....92
3.5 MEASUREMENT INSTRUMENTS....92
3.5.1 INTERVIEWS....92

3.5.2 INTERVIEW SCHEDULE....95
3.5.2 AUDIOTAPE RECORDINGS....102
3.6 PROCEDURE....102
3.6.1 PILOT STUDY....102
3.6.2 RECRUITMENT....103
3.6.3 IMPLEMENTATION OF INTERVIEWS....104
3.7 TRUSTWORTHINESS AND VALIDITY....105
3.7.1 CREDIBILITY....106
3.7.2 DEPENDABILITY....106
3.7.3 CONFIRMABILITY....107
3.7.4 TRANSFERABILITY....107
3.8 RELIABILITY....108
3.9 DATA ANALYSIS....109
3.9.1 QUALITATIVE DATA....109
3.9.2 QUANTITATIVE DATA....111
3.10 ASSUMPTIONS....112
3.11 ETHICAL CONSIDERATIONS....113
3.12 WEAKNESS OF STUDY....115
3.13 STRENGTHS OF STUDY....116

CHAPTER FOUR (ANALYSIS, RESULTS/FINDINGS & DISCUSSION)....118
4.1 INTRODUCTION....119
4.2 GROUP A-GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC (GESC)....120
4.3 DEMOGRAPHIC DATA AND PERSONAL HISTORY....122
4.4 KNOWLEDGE OF LYNCH SYNDROME....136
4.5 GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC....149
4.6 SATISFACTION WITH THE GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC (GESC)175
4.7 COMMUNICATION WITHIN THE FAMILY....181
4.8 GENERAL HEALTH OF PARTICIPANT....194
4.9 RESEARCH....205
4.10 SUMMARY OF RESULTS/FINDINGS FOR GROUP A....206
4.11 GROUB B-PREDICTIVE GENETIC TESTING PROGRAMME (PT)....209
4.12 DEMOGRAPHIC DATA AND PERSONAL HISTORY....212
4. 13 GENETIC COUNSELLING PERSPECTIVES AND SATISFACTION....219
4. 14 POST-PREDICTIVE TEST RESULT....230
4. 15 SUMMARY OF RESULTS/FINDINGS FOR GROUP B....243

CHAPTER FIVE (CONCLUSION)....245
5.1 CONCLUSION....246
5.1.1 GENETIC AND ENDOSCOPIC SURVEILLANCE PROGRAMME (GROUP A)....246
5.1.2 PREDICTIVE GENETIC TESTING PROGRAMME (GROUP B)....248

CHAPTER SIX (RECOMMENDATIONS)....250
6.1 RECOMMENDATIONS....251
6.1.1 RECOMMENDATIONS FROM THE PARTICIPANTS ATTENDING FOR SURVEILLANCE AT THE GESC (GROUP A)....251

6.1.2 RECOMMENDATIONS FROM THE PARTICIPANTS ATTENDING FOR GENETIC COUNSELLING AND PT (GROUP B) 252
6.1.3 RECOMMENDATIONS IDENTIFIED THROUGH THE STUDY 253

REFERENCES 257
APPENDIX 1 (PT PROTOCOL) 303
APPENDIX 2 (INFORMATION SHEET FOR TELEPHONIC CONTACT) 307
APPENDIX 3 (INFORMATION SHEET AND CONSENT FORM) 309
APPENDIX 4a (INTERVIEW SCHEDULE FOR GROUP A) 312
APPENDIX 4b (INTERVIEW SHEDULE FOR GROUP B) 321
APPENDIX 5 (ETHICAL APPROVAL) 328
APPENDIX 6 (SOCIAL SECURITY GRANTS IN SOUTH AFRICA) 331
APPENDIX 7 (GENETIC TESTING FOR AT-RISK FAMILY LETTER) 333
APPENDIX 8 (LEAVE OF ABSENCE LETTER) 335

FIGURE NUMBER

PAGE

FIGURE A: Map of Southern Africa....xxiii
FIGURE 1: Timeline of the key events leading to the establishment of the outreach (mobile) Genetic and Endoscopic Surveillance Clinic. 3
FIGURE 2: A five-year overview (2004-2008) of the attendance rate to the Genetic and Endoscopic Surveillance Clinic....4
FIGURE 3: Contribution of Lynch syndrome to the colorectal cancer burden....16
FIGURE 4: The geographic location of the Western and Northern Cape in comparison to the other provinces in South Africa 78
FIGURE 5: An outline of the methodology used during the study....87
FIGURE 6: The interconnectivity of Group A and Group B interview schedules....96
FIGURE 7: The number of years from the time of the genetic test to the research interviews (n=83) ..121
FIGURE 8: Level of education as defined by clinic (outreach versus hospital) among those participants aged 20 years and older 124
FIGURE 9: Comparison of unemployment rates for the outreach (n=52) and hospital (n=28) participants....125
FIGURE 10: Comparison of the level of household income between the outreach (n=52) and hospital (n=28) group 127
FIGURE 11: Type and count of social aid received from government 128
FIGURE 12: Comparison of the number of individuals per household of the outreach (n=52) and hospital group (n=28). 129
FIGURE 13: Type and frequency of the parental cancer of the participants in Group A....130
FIGURE 14: Comparison of participant's number of first-degree relatives with colorectal cancer 131
FIGURE 15: Comparison of uptake rate of genetic testing among the outreach and hospital participants' siblings....132
FIGURE 16: Comparison of uptake rate of genetic testing among the outreach and hospital participants' children 133
FIGURE 17: Comparison of cancer history of participants attending either the outreach or hospital clinic (n=80). 133
FIGURE 18: Age of onset of first colorectal cancer (n=16).. 135
FIGURE 19: The number of correct answers per item of the level of knowledge questionnaire (n=80)136
FIGURE 20: Relationship between education and knowledge (as measured by the Domanska scale)140
FIGURE 21: Level of knowledge per adherence group... 141
FIGURE 22: Average knowledge per number of years attending GESC.. 143
FIGURE 23: Knowledge of colorectal cancer symptoms among participants (n=80).....144
FIGURE 24: Recall of inherited risk to first-degree relatives....144
FIGURE 25: Frequency of missed appointments per age group..... 152
FIGURE 26: Self-reported adherence versus actual adherence....153
FIGURE 27: Major facilitators of adherence (items are not mutually exclusive) 164
FIGURE 28: Major barriers to adherence (items are not mutually exclusive)..... 165
FIGURE 29: Adherence per age group (n=80)..... 171
FIGURE 30: A plot of the component loadings of the six items on the GESC satisfaction scale 177
FIGURE 31: Plot of category points of the six items on the GESC satisfaction scale....178
FIGURE 32: Individuals to whom the participants disclosed their PT results....186

FIGURE 33: Communication of risk implications (subsequent to receiving mutation-positive test result) within the family..... 188
FIGURE 34: Discussion of PT or cancer-related risk with children..... 190
FIGURE 35: Frequency of discussion of Lynch syndrome-related topics (n=80).....191
FIGURE 36: Information aids required by participants (n=80)..... 192
FIGURE 37: Communication pathways within Lynch syndrome families attending the GESC 193
FIGURE 38: Plot of category points of the four items (F7a-F7d) on CWS..... 202
FIGURE 39: A plot of the component loadings of the four items (F7a-F7d) combined with 'knowledge' and 'adherence'..... 203
FIGURE 40: Level of education among participants entering into PT..... 213
FIGURE 41: Employment and unemployment rates among participants entering into PT (n=33)..... 214
FIGURE 42: The level of household income for the PT participants (n=33)..... 215
FIGURE 43: Exposure to colorectal cancer (CRC) within family.....216
FIGURE 44: Attitude to termination of pregnancy (TOP) in mutation-positive fetus.....217
FIGURE 45: Satisfaction with the process and content of genetic counselling according to the GCSC (n=33).....220
FIGURE 46: Total score per participant on the genetic counselling satisfaction scale..... 221
FIGURE 47: A plot of the component loadings of the demographic variables and the six items (3a-3f) on the genetic counselling satisfaction scale..... 223
FIGURE 48: A plot of the component loadings of the items education and ethnicity..... 224
FIGURE 49: Period of awareness prior to entering into PT..... 225
FIGURE 50: Perceived emotional reactions to outcome of PT.... 228
FIGURE 51: Comparison of mean DUKE-AD score for mutation-positive and mutation-negative participants at assessment time points before and after disclosure of PT results..... 235
FIGURE 52: Comparison of mean scores of cancer-related worry for mutation-positive and mutation-negative participants at assessment time points before and after disclosure of PT 236
FIGURE 53: Marginal means of the DUKE-AD measure per mutation-status.... 240
FIGURE 54: Marginal means of the CWS measure per mutation-status 243

TABLE NUMBER

PAGE

TABLE 1: The characteristics which typify Lynch syndrome.....19
TABLE 2A: Amsterdam criteria I..... 21
TABLE 2B: Amsterdam criteria II..... 22
TABLE 2C: Revised Bethesda Guidelines for testing of colorectal tumours for microsatellite instability.... 23
TABLE 3: Incidence of Lynch syndrome by geographical region..... 30
TABLE 4A: Lynch syndrome tumour spectrum: published studies of the lifetime cancer-related risk per mismatch repair gene mutation carriers..... 46
TABLE 4B: Lynch syndrome tumour spectrum: published studies of the lifetime cancer-related risk per mismatch repair gene mutation carriers..... 47
TABLE 5: Adherence grouping (1-5) as used to define and select the sample frame of the study (Group A)..... 90
TABLE 6: Number of interviews conducted for Group A and Group B.....91
TABLE 7: Sociodemographic characteristics of the study participants (n=80)..... 122
TABLE 8: Reasons for not completing or continuing with schooling and/education (n=80)..... 125
TABLE 9: Reasons for unemployment (n=80)..... 126

TABLE 10: Occupation categories (n=80)..... 126
TABLE 11: Parental cancer history profile..... 129
TABLE 12: Age of participant at parental cancer/cancer diagnosis.... 130
TABLE 13: Number of siblings and children per participant (n=80)..... 131
TABLE 14: Characteristics of the affected participants within Group A (n=16)..... 134
TABLE 15: Description of items displayed in Figure 19..... 136
TABLE 16: The number of participants with correct answers to the eight items on the Domanska et al (2009) scale (n=80)..... 136
TABLE 17: Effects of the source of information on the level of knowledge (n=80)..... 138
TABLE 18: Frequency of individuals seeking more information on Lynch syndrome per information source (n=80)..... 139
TABLE 19: Knowledge score per gender of participant (n=80)..... 140
TABLE 20: The effect of gender on average knowledge score..... 140
TABLE 21: Classification of the number of years within the GESC.... 141
TABLE 22: Level of knowledge per number of years within GESC..... 142
TABLE 23: The relationship between length of time at GESC and knowledge (n=80)..... 142
TABLE 24: Bonferroni post hoc test (number of years within GESC and average knowledge)..... 143
TABLE 25: Emotional response to hearing information of children being at risk for colorectal cancer..146
TABLE 26: Perceived lifetime risk of developing colorectal cancer..... 148
TABLE 27: Transport and travel time to Genetic and Endoscopic Surveillance Clinic (n=73)..... 149
TABLE 28: Travel time and mode of transportation for participants attending for surveillance but missing one or more colonoscopies (n=54)..... 150
TABLE 29: Travel time and adherence group for participants utilising free hospital transport (n=21)...151
TABLE 30: Knowledge of participants using free hospital transport (n=21)..... 151
TABLE 31: Gender cross-tabulated with adherence and travel time.... 152
TABLE 32: Employment status per age group (n=18)..... 152
TABLE 33: Adherence to recommended screening guidelines (n=80)..... 153
TABLE 34: Demographic data on seven participants who had never had a colonoscopy.... 155
TABLE 35: Personal experience of surveillance (n=80)..... 155
TABLE 36: Cross-tabulation of pain and adherence (n=73)..... 161
TABLE 37: Rating frequencies per item on the facilitator and barriers to adherence scale (n=80)..... 164
TABLE 38: Additional barriers to adherence (specific to the GESC) (n=61)..... 167
TABLE 39: Adherence to recommended screening guidelines defined by clinic (outreach versus hospital)..... 167
TABLE 40: Adherence to recommended screening guidelines (compliant versus non-compliant) defined by clinic (outreach versus hospital)..... 168
TABLE 41: Cross-tabulation of education with adherence group (n=80)..... 168
TABLE 42: Cross-tabulation of gender and adherence (n=80)..... 169
TABLE 43: Participant adherence cross-tabulated with gender of affected and unaffected parent (n=80)..... 169
TABLE 44: Cross-tabulation of adherence and referral type (n=80)..... 170
TABLE 45: Adherence per age group (n=80)..... 170
TABLE 46: Attitude to surveillance following a family member's cancer cross-tabulated with actual adherence (n=80)..... 172
TABLE 47: The relationship between adherence and the level of care involvement..... 172
TABLE 48: The occurrence of categories of a subset of variables relating to colonoscopic screening.174
TABLE 49: The rating frequencies per item on the GESC satisfaction scale (n=80)..... 175

TABLE 50: Component loadings per item of a two dimensional CAT-PCA on the GESC satisfaction scale (n=80)..... 176
TABLE 51: Rating per item on the GESC satisfaction scale for P59.... 176
TABLE 52: Understanding of familial risk per gender of participants (n=80).....179
TABLE 53: Questions addressed at GESC per gender of participants (n=80).....179
TABLE 54: Cross-tabulation of knowledge with understanding of a familial risk (n=80).... 180
TABLE 55: Knowledge cross-tabulated with referral type (n=80)..... 180
TABLE 56: Emotional reaction to receiving a mutation-positive test result.... 182
TABLE 57: Participants' source of emotional support subsequent to receiving a mutation-positive test result.... 185
TABLE 58: Informing family about risk implications after receiving a mutation-positive test result.... ...188
TABLE 59: Lifestyle risk behaviours of participants (n=80).....195
TABLE 60: Frequency of rating items of DUKE-AD scale (n=80)..... 196
TABLE 61: Frequency of rating the sum of each item of DUKE-AD (n=80)..... 197
TABLE 62: Interpretation of overall scores on DUKE-.... 197
TABLE 63: The number of individuals with excessive symptoms of anxiety and depression (n=80).....198
TABLE 64: Characteristics of participants with excessive symptoms of anxiety and depression (n=26)..... 199
TABLE 65: Number of participants with excessive symptoms per age group (n=26).... 200
TABLE 66: Frequency of rating items of the CWS (n=80)..... 201
TABLE 67: Component loadings per item of a two dimensional CAT-PCA... 201
TABLE 68: Re-coding of rating items on the CWS to reflect the two new variables (thoughts/worries and mood/performance).....203
TABLE 69: Cross-tabulation of cancer-related thoughts with number of first-degree relatives with cancer.... 204
TABLE 70: Cross-tabulation of mood disturbances with number of first-degree relatives with cancer..204
TABLE 71: Frequency of cancer-related thoughts and mood disturbances among affected (n=16) and unaffected (n=64) participants.... 205
TABLE 72: The nature and frequency of the involvement in longitudinal and cross-sectional research studies.....205
TABLE 73: Sociodemographic characteristics of the PT study participants (n=33)..... 212
TABLE 74: Occupation categories for participants entering into PT (n=33).....214
TABLE 75: Number of siblings and children per participant (n=33)..... 216
TABLE 76: Rating frequencies per item of information discussed during genetic counselling (n=33)...219
TABLE 77: The rating frequencies per item on the genetic counselling satisfaction scale (n=33).... 220
TABLE 78: Demographic variables used in the analysis of the level of satisfaction with genetic counselling (n=33).....222
TABLE 79: Component loadings per item of a two-dimensional CAT-PCA involving participant demographics and the genetic counselling satisfaction scale (n=33).....222
TABLE 80: The influence of the level of exposure to colorectal cancer on the time to presenting for PT (n=26).... 226
TABLE 81: Life event triggering request for PT (n=33).....226
TABLE 82: Rating frequencies per item of factors affecting decision to undergo PT (n=33)..... 227
TABLE 83: Cross-tabulation of the understanding of PT and selected participant characteristics (n=33)..... 228
TABLE 84: The comparison of perceived PT result to actual PT result (n=22).....229
TABLE 85: PT result per gender of the participants (n=22)..... 230
TABLE 86: Specific Lynch syndrome mutation among mutation-positive cohort (n=11).....231
TABLE 87: Characteristics of participants who did not return for their genetic test result (n=10)..... 231

TABLE 88: A subset of categories relating to satisfaction with the PT process (n=22).....232
TABLE 89: Emotional reaction following predictive test result disclosure (n=22).....234
TABLE 90: Multivariate tests at assessment time points on the DUKE-AD scale before and after disclosure of PT results including the effect on mutation-status.....238
TABLE 91: Tests of within-subject effects.....238
TABLE 92: Tests of between-subject effects.....239
TABLE 93: The relationship between DUKE-AD score and mutation-status over assessment time points.....239
TABLE 94: The relationship between CWS score and mutation-status when DUKE-AD key is applied.....240
TABLE 95: Multivariate tests at assessment time points on CWS before and after disclosure of PT results including effect on mutation status.....241
TABLE 96: Mauchly's test of sphericity (tests of within-subjects affects).....241
TABLE 97: Tests of within-subject effects.....242
TABLE 98: Tests of between-subject effects.....242
TABLE 99: The relationship between CWS score and mutation-status over assessment time points..242

PHOTOGRAPH NUMBER

PAGE

PHOTOGRAPH 1: Typical 'matjieshuis' in Nourivier, Northern Cape.....123
PHOTOGRAPH 2: Outside toilet in Buffelsrivier, Northern Cape.....157
PHOTOGRAPH 3: Makeshift bucket toilet in Nourivier, Northern Cape.....158

LIST OF ABBREVIATIONS

BRAF	V-raf murine sarcoma viral oncogene homolog B1
BRCA 1	Breast Cancer susceptibility gene 1
BRCA 2	Breast Cancer susceptibility gene 2
CA-125	Cancer antigen 125
CRC	Colorectal cancer
CRCGC	Colorectal cancer genetic co-ordinator
CUM	Cumulative lifetime risk
CWS	Cancer worry scale
DG	Disability grant provided by the state
DNA	Deoxyribonucleic acid
DBE	Double balloon endoscopy
DUKE	DUKE Anxiety and Depression scale
FAP	Familial adenomatous polyposis
FDR	First-degree relatives
GESC	Genetic and Endoscopic Surveillance Clinic
GP	General Practitioner
GSH	Groote Schuur Hospital
HBOC	Hereditary breast and ovarian cancer
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
MLH1	MutL homologue 1
MSH2	MutS homologue 2
MSH6	MutS homologue 6
PMS2	Postmeiotic Segregation 2
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
ICG-HNPCC	International Collaborative Group on HNPCC
IHC	Immunohistochemistry
InSiGHT	International Society for Gastrointestinal Hereditary Tumour
LS	Lynch syndrome
MMR	Mismatch repair
MSI	Microsatellite instability
MTS	Muirr-Torre syndrome
NC	Northern Cape
n.d	No date available for referencing source
P	Participant
PT	Predictive testing
SA	South Africa
SBC	Small bowel cancer
TOP	Termination of pregnancy
TVU	Transvaginal ultrasound
UCT	University of Cape Town

UK	United Kingdom
USA	United States of America
UTC	Urinary tract cancer
VCE	Video capsule endoscopy
WC	Western Cape

GLOSSARY

Adenoma: A benign tumour that develops from epithelial tissue.

Adenocarcinoma: A malignant tumour that develops from epithelial cells, originating in glandular tissue.

Autosomal dominant inheritance: The expression of a gene in the heterozygous state, located on an autosome.

Colonoscopy: A medical procedure which permits the visual examination of the entire colon, using an illuminated flexible endoscope.

Colectomy: Surgical removal of part of or the entire colon.

DNA: The genetic material of a cell which allows for the transmission of genetic information from one generation to the next.

Extracolonic: Developing outside of the colon.

Founder effect: Loss of genetic variation as a result of a new population being established by a few members from the larger population – a type of genetic drift.

Gene: A sequence of DNA that codes for a particular protein.

Germline mutation: A heritable mutation in the lineage of germ cells. These mutations are transmitted to offspring.

HNPCC/Lynch syndrome: An autosomal dominant cancer syndrome characterised by early-onset colorectal cancer with an absence or limited number of colonic polyps, usually occurring in the proximal colon. There is also a predisposition to other extracolonic cancers.

Huntington Disease: An autosomal dominant neurodegenerative disorder involving chorea, cognitive decline and dementia.

Ileorectal anastomosis: Surgery involving the removal of the colon, which leaves the rectum intact by attaching the ileum to the rectum.

Metachronous: Tumours occurring more than six months after surgical resection for colorectal cancer.

Mutation: An alteration in the DNA sequence or chromosome structure, damaging the function of a gene and may be disease-causing.

Mutation-negative: An individual who does not have a gene mutation. If an individual is mutation-negative for a specific genetic disorder, they are not at-risk of developing the disorder.

Mutation-positive: An individual who does have a gene mutation. If an individual is mutation-positive for a specific genetic disorder, they are at-risk of developing the disorder.

Polyp: A mucousal protuberance into the lumen of the colon.

Predictive testing: A form of genetic testing which is capable of identifying the presence of a mutation in a gene prior to the individual developing any symptoms of the disease. The detection of the genetic mutation does not necessarily mean the individual will definitely develop the disorder.

Predisposition: Having a greater than average risk of developing a disease as a result of an inherited gene mutation.

Prophylactic surgery: Surgery performed before a particular phenotype manifests itself in the individual.

Proximal: Ascending and transverse colon.

Rectum: The last 10-12 centimetres of the digestive tract before the anus.

Rural: an area consisting of a commercial farm, small settlement or rural village beyond an urban area.

Sigmoid colon: The area of the colon that comes after the descending colon and before the rectum.

Sigmoidoscopy: A medical procedure involving the examination of the rectum and the lower portion of the colon (sigmoid colon) through an illuminated sigmoidoscope.

Synchronous: Multiple tumours seen at or within six months of surgical resection for colorectal cancer.

Tumour: An abnormal mass of tissue resulting from excessive cell division. This may be benign (non-cancerous) or malignant (cancerous).

Urban: An area that includes a town, city or metropolitan area.

(The terms in the glossary have been adapted from Jorde et al 2006 and Naussbaum et al 2004).

PREFACE

This work will refer to the following terms when describing the study participants and the population of South Africa.

Mixed Ancestry/Coloured Population: Refers to a heterogeneous group of persons from a mixed racial ancestry. While the label 'Coloured' is a contentious term, it is still used to describe the mixed race population, descended from slaves brought in from East and Central Africa, the indigenous Khoisan, indigenous Africans and the White European settlers. A marked regional concentration of Coloured people exists within the Western Cape and Johannesburg.

The majority of individuals within the Coloured group speak Afrikaans (a language similar to Dutch).

Black African population: In accordance with accepted terminology, this group of individuals are referred to as the 'Black population' of South Africa. The Black population is neither culturally nor linguistically homogenous, with nine of the countries official 11 languages being African. The group includes the Nguni, South-Tswana, Tsonga and the Venda.

Caucasian/White population: The white population descends largely from the colonial immigrants of the late 17th to 19th century and includes settlers from Netherlands, Germany, France and England. Linguistically, they are divided into Afrikaans- and English-speaking groups.

Certain terms have been used interchangeably in this work, and include: **'adherence'** and **'compliance'**. These terms both describe a patient's fulfilment of the healthcare professional's recommendation, which in this work pertains to the regular attendance of colonoscopic screening. **'Non-adherence'** and **'non-compliance'** both correspond to non-attendance or irregular attendance.

The terms **'mutation-positive'** and **'carrier'** are both used to describe an individual with an inherited predisposition to Lynch syndrome, and **'mutation-negative'** and **'non-carrier'** an individual without the predisposition. Furthermore, '**findings'** and '**results'** are used interchangeably within Chapter Four (analysis, findings/results and discussion) and refers to both the qualitative and quantitative data.

'Client' and **'counselee'** are also used interchangeably and these terms are used to describe the individuals attending for genetic counselling.

Photos have been included in the results and discussion section to illustrate the living conditions, where a written report would not have sufficed. The referencing format used in this work has drawn on the guidelines of Neville (2007).

Figure A. Map of Southern Africa. The outreach Genetic and Endoscopic Surveillance Clinic runs annually from Cape Town (in the Western Cape) along the western coast to the alluvial diamond mining village of Kleinsee. The route is closely interlinked to the location of known Lynch syndrome families residing in the Western and Northern Cape provinces. The red crosses on the map indicate the location of the clinics where the endoscopic procedures are performed.

CHAPTER ONE: INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1 INTRODUCTION

Lynch syndrome (LS) is an inherited predisposition to early-onset colorectal and endometrial cancer, caused by mutations in DNA mismatch repair genes (Lynch et al 1998). It is the most common form of hereditary colorectal cancer (CRC) and has a worldwide prevalence of 1 in 3 000 persons (Young 2001).

The first clinical description of LS in South Africa (SA) was in 1985 (Goldblatt et al 1990). The diagnosis was based on an affected 30 year old man who had a cancer of his colon resected at the age of 19 years, and a detailed family pedigree showing autosomal dominant inheritance over three generations (Ramesar et al 2000). The identification of LS in this family occurred prior to molecular genetic testing being available in SA. All blood relatives of the proband were therefore at an empirical risk of developing LS, as identified through their lineage (Anderson et al 2007; Goldblatt et al 1990).

Surveillance guidelines for LS differ from those recommendations for population based colon cancer risk, in general. A full colonoscopy is recommended at a young age because of a higher risk for right-sided tumours in LS compared to the involvement of the rectum and sigmoid colon, more commonly seen in sporadic cancer (Vasen et al 1999). The younger age of onset warrants earlier screening, and the higher incidence of a secondary metachronous or synchronous malignancy, a shorter interval time between colonoscopies. Current guidelines propose that the surveillance of the colon, in at-risk individuals, be initiated at the age of 20-25 years and be repeated every one to three years (Vasen et al 1991; Vasen et al 1999). In SA, colonoscopic screening for LS is recommended biannually until 30 years of age and, annually thereafter (Goldberg et al 1998).

Because of an established founder effect, it is now recognised that many individuals at a high risk of developing LS are clustered in specific areas in the Western Cape (WC) and Northern Cape (NC) Province of SA (Goldberg et al 1998). Access to surveillance services and the provision of ongoing management at the afore-mentioned intervals create major logistical difficulties, as most of those at risk are located in remote areas of these provinces (Anderson et al 2007). In an attempt to facilitate access, an outreach endoscopic programme was initiated and runs in conjunction with the colonoscopic services offered in the established endoscopic unit at Groote Schuur Hospital (GSH) in Cape Town in the WC Province (Goldblatt et al 1990). This outreach service is intended to provide an annual mobile service in small district hospitals and clinics. All of the surveillance equipment is transported, and trained staff travel from Cape Town, along the western coast of SA to the Namibian border, to conduct such a surveillance clinic (Figure A). In addition to the surveillance service, the mobile unit created a platform to recruit family members, based on empirical risk, into research programmes. This research led to the discovery of the causative mutation in 1996 by the University of Cape Town (UCT) Human Genetics group and to the establishment of a predictive testing (PT) and counselling programme which was integrated into the mobile endoscopic unit's service in 1996/1997 (Figure 1) (Goldberg et al 1998; Ramesar et al 2000).

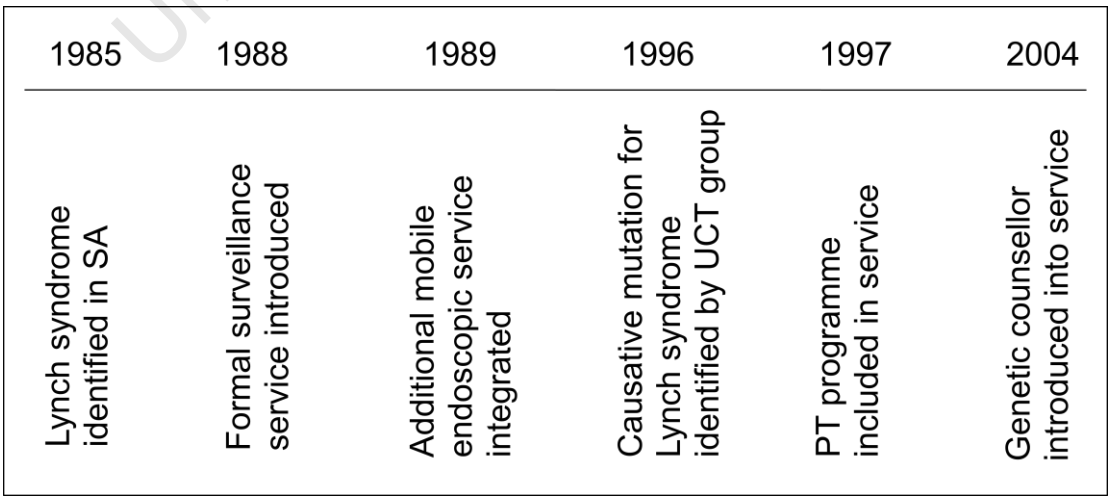

Figure 1: Timeline of the key events leading to the establishment of the outreach (mobile) Genetic and Endoscopic Surveillance Clinic.

Genetic testing is capable of optimally utilising limited surveillance expertise and equipment in LS families, and can greatly reduce the demand of colonoscopic procedures at hospitals and the efforts of the yearly outreach endoscopic mobile clinic (Goldberg et al 1998). Mutation-positive individuals (at a high risk of developing CRC) should receive regular endoscopic surveillance and mutation-negative individuals, should undergo screening according to general population guidelines (Lynch et al 1998). Essentially, regular endoscopic surveillance in individuals at risk of developing LS can prevent CRC by removing the precancerous lesion or enabling the treatment of cancer at an early stage (Järvinen et al 2000). The importance of access to a surveillance service is thus crucial for at-risk individuals and has been fundamental in the establishment and maintenance of a mobile genetic and endoscopic surveillance service.

Unfortunately, attendance at this outreach service has been declining. In 2008, approximately half the patients scheduled to attend on a single outreach visit, did not attend. This declining pattern is depicted in Figure 2 which illustrates the attendance rate (total number of expected visits compared to the total number seen) over the five-year period prior to the commencement of this research study in 2009.

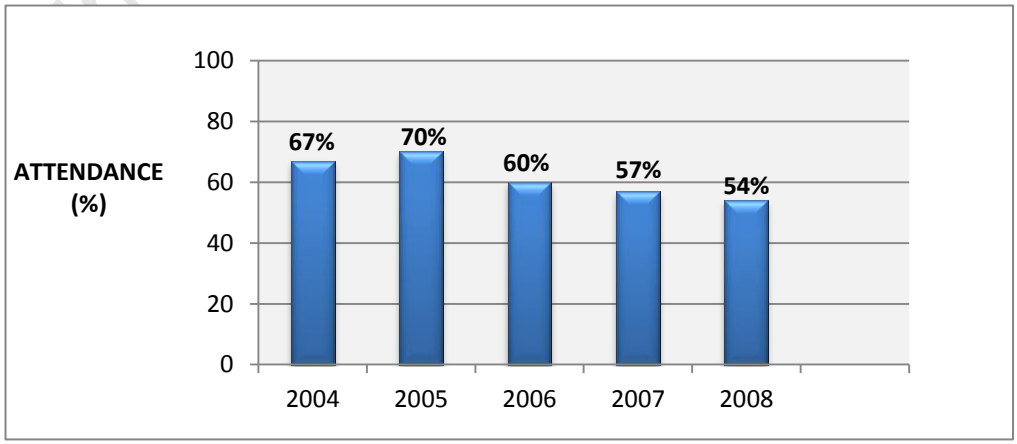

Figure 2: A five-year overview (2004-2008) of the attendance at the Genetic and Endoscopic Surveillance Clinic.

1.2 SIGNIFICANCE OF THE STUDY

Intervention strategies, dedicated to improving health and preventing cancer, are only as effective as the number of patients they serve. Clearly, offering regular colonoscopic screening to individuals at risk for LS, at the outreach clinic, is not sufficient to prevent or treat cancer. In 2008, 46% of the known at-risk population did not attend their appointments (Figure 2). There is thus an obvious need to evaluate factors affecting the access, utilisation and satisfaction with this service, from the perspective of the service users.

The evaluation of genetic counselling services, in general, is not a unique aspect in the literature and the most common criteria assessed include: knowledge, risk comprehension or recall, psychological distress, patient satisfaction and reproductive decision-making (Bernhardt et al 2000; Bjorvatn et al 2007; Collins et al 2000; Kessler 1989; Michie et al 1997; Pilnick and Dingwall 2001). These measures have been used to assess the services in order to improve the process of genetic counselling and care provided to individuals concerned about a genetic risk.

The Genetic and Endoscopic Surveillance Clinic (GESC) has been in operation for more than a decade, however, few changes have been implemented during this time and no formal evaluation has previously been undertaken. The value of conducting an investigation into the effectiveness of the current service, the ability to meet the patients‘ needs and the potential to identify areas amenable to improvement is obvious when considering the declining attendance (Figure 2). In order to conduct this investigation, a broad social profile of the individuals attending for surveillance (after receiving a mutation-positive test result) and of those entering into the PT programme is needed to appraise the GESC. Furthermore, comparison between the service offered in an established centre and the outreach clinic should be made to allow for a more comprehensive evaluation.

Extensive research has also been conducted on LS. The avenues that have been investigated and for which a great deal of information is available include: the molecular cause, clinical features, lifetime cancer-related risks and the management and surveillance options and benefits. Since the identification of the molecular cause of the disease, genetic testing, PT programmes, genetic counselling and the psychosocial impact of the condition on the individual as well as the family, have been assessed comprehensively in western developed countries. However, data pertaining to LS within a developing country and especially focused on individuals from a low socio-economic background are sparse. Therefore, this research project intended to evaluate the service experienced by individuals involved in the PT programme as well as the satisfaction with the surveillance service offered to patients with LS, within this specific context. By providing further details of the individuals‘ socio-economic environment, greater insight into the impact of these factors on their clinical, social and psychological aspects, can be gained.

This study aimed to identify and provide further insight into patients‘ needs and their experience of the healthcare service offered. By gaining an understanding of the facilitators and barriers to attendance, it was hoped to increase the level of patient satisfaction as well as the uptake of genetic testing and compliance with screening regimens. Furthermore, knowledge derived from the investigation can be extrapolated to developing policy guidelines for the establishment of similar services in the other provinces of SA (currently the outreach service is only offered in the Western and Northern Cape Province).

1.3 AIMS OF THE STUDY

The aims of this study were:

- To appraise the GESC from the users‘ perspective using face-to-face interviews to ascertain their experiences and level of satisfaction with the surveillance and PT aspects of the clinic;

- To measure the level of the adherence to recommended surveillance screening guidelines;
- To determine the impact of socio-economic status, education, physical barriers and psychosocial factors on adherence to the recommended surveillance programme;
- To determine the uptake of PT among participants and their family members;
- To identify and explore the referral pathways and communication networks, leading to attendance at the GESC.

1.4 OBJECTIVES OF THE STUDY

The objectives of the study were divided into four categories:

1.4.1. BACKGROUND INFORMATION

- To compile a profile of the participants attending the GESC;
- To measure the extent of adherence to the recommended screening guidelines;
- To identify facilitators and barriers affecting the level of adherence to the recommended surveillance programme;
- To compare uptake rates of PT among family of the participants (first-degree relatives);
- To explore the reasons for the uptake of genetic testing among PT participants;
- To explore the reasons for non-uptake of genetic testing among PT participants.

1.4.2. UNDERSTANDING, EXPERIENCE, AND SATISFACTION WITH THE SERVICE DELIVERED

- To identify the sources of information relating to the participant‘s knowledge of LS;

- To explore the level of genetic knowledge of LS amongst high-risk individuals attending the service;
- To measure the level of satisfaction with the endoscopic surveillance service;
- To measure the level of satisfaction with genetic counselling and the PT programme;
- To describe the psychological impact of participating in the endoscopic surveillance and the PT programme.

1.4.3. REFERRAL PATHWAYS AND COMMUNICATION NETWORKS LEADING TO ATTENDANCE AT THE SERVICE

- To identify and investigate the referral pathways to the service;
- To determine the accessibility of the service;
- To determine to who the participant discloses his or her genetic test result and the reasons for the choice of the specific person(s);
- To investigate the transmission of information about genetic risk within the immediate family;
- To explore the participants‘ experience of informing family members about the genetic risk;
- To determine the role of the healthcare providers in: (1) maintaining confidentiality with the individual‘s genetic test results and (2) the healthcare provider‘s responsibility to inform family members of their at-risk status.

1.4.4. IMPROVE SERVICE OFFERED TO PARTICIPANTS AND THEIR FAMILIES

- To explore the participants‘ experience of their involvement in previous research and attitude to involvement in future research programmes;
- To determine the recommendations the users make to improve the service;
- To explore the support systems available to participants and their families;

- To determine the general health of the participant to facilitate appropriate referral if bowel-related concerns are identified.

1.5 OUTLINE OF RESEARCH DESIGN AND METHODOLOGY

The study used a combination of qualitative and quantitative methods within a phenomenological research design. Two groups of participants were interviewed utilising a semi-structured interview schedule. The first group included individuals who had received a mutation-positive test result and were recommended to adhere to regular colonoscopic screening. The second group involved interviews with individuals entering the PT programme.

A cross-sectional approach was used to facilitate the gathering of information from participants required to attend for regular screening, while a longitudinal approach, consisting of three interviews (prior to PT, post PT and one month after PT result was received) was used for those individuals embarking on the PT process. Interviews were conducted within the participant‘s homes, a private room at the clinic or a private venue of the participant‘s choice.

1.6 ORGANISATION OF THE STUDY

Chapter Two: an overview of the current literature on LS, placing it in the context of developments in science, medicine, psychology and genetic counselling is provided. It explores all the published literature relating to the genetic and surveillance services for LS as well as describing the development of a mobile GESC in the Western and Northern Cape. The end of the chapter presents further information on the historical and current socio-economic background of individuals affected by and at-risk of developing LS in SA.

Chapter Three: the methodology design and outline of the research process is discussed. The steps involved in selecting participants are described and the validity and reliability/trustworthiness of the measurement instrument is

discussed. A description of the data collection and analysis is provided while addressing ethical principles.

Chapter Four: the results of the research study are presented and discussed. Analysis and discussion are included in the same chapter to prevent unnecessary repetition of information and to aid the clarity and understanding of the results of the study. This form of co-presenting results and the discussion is in line with recommendations for qualitative research (McMillan and Schumacher 2001).

Chapter Five: the main findings as summarised in the conclusion of the study are described.

Chapter Six: aspects to improve the GESC are identified.

"I inherited two things from my grandmother: a delicate Royal albert tea service, and a genetic condition called HNPCC. I would have preferred to have just the fine china, really. My grandmother's gene gives me an 80% chance of getting colorectal cancer, 40% chance of getting womb cancer, and slightly lower odds on a veritable smorgasbord of other cancers" (Participant 53).

CHAPTER TWO: LITERATURE REVIEW

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

The literature review presents an extensive overview of CRC, with specific reference to LS, including information on the natural history, epidemiology, clinical features, clinical and molecular diagnosis, management and surveillance recommendations. The psychosocial impact of the disease, predictive testing, genetic counselling, family communication and satisfaction with genetic services are also addressed.

As it is essential to understand the context from which the study cohort originated and within which the research was conducted a brief introduction of the history of SA is provided. The effect the _apartheid' political system had on different population groups of the nation, through its discriminatory legislature, is also briefly described. The ensuing impact that this has had on the health care system is discussed to ensure that the reader is familiar with the medical background and social environment of the families in the study.

Literature searches were conducted using the following terms: _Lynch syndrome', _HNPCC', _hereditary colorectal cancer', _genetic testing', _predictive testing', _genetic susceptibility testing', _testing for cancer susceptibility', _uptake', _genetic counselling', _psychological impact', _psychosocial impact', _adverse outcomes', _distress', _Lynch syndrome/ HNPCC management', _surveillance', _screening', _risk', _at-risk', _disclosure', _communication', _patient satisfaction', _assessment' and _population statistics' on Pubmed, ScienceDirect, Ebscohost, CancerLit, Ovid, wwwstatssa.gov.za, CINHL, Google Scholar, African studies library and UCT (medical and main) libraries. The literature review mainly refers to studies conducted in the United Kingdom (UK), Europe, United States of America (USA), Canada and Australia as a result of the paucity of published information available from developing countries in general and SA in particular.

2.2 COLORECTAL CANCER (CRC)

CRC is the most common visceral cancer in developed countries and the second most-frequent malignancy to affect both men and women in western civilisations. The estimated annual worldwide incidence of CRC is escalating and has recently reached a figure of 1, 023 152, with approximately half a million deaths attributed to this disease each year (Parkin et al 2005).

CRC is typically associated with a westernised diet and sedentary lifestyle, thus developed countries and affluent societies, particularly, North America and Western Europe illustrate higher incidence rates than those in Asia and Africa. While Africa is classified as a developing country, SA is more reflective of a western society, reporting among the highest cancer rates of the continent. The South African Cancer Registry for 1998-1999 indicates that the age-standardised incidence rate for CRC is 9.74 per 100 000 inhabitants for males and 6.61 for females. The lifetime risk of developing bowel cancer, in SA, is 1 in 91 for men and 1 in 134 for women (National Cancer Registry 1999). The epidemiology of CRC among White SA's, specifically, appears to follow the classic western trend (Cronje et al 2009). In contrast the risk of CRC is reported to be lowest among Black men and women compared to the other population groups (Mqoqi et al 2004; Walker and Segal 2002).

Of great concern is that the overall incidence of CRC in SA has increased dramatically over the last decade. In 1989, CRC featured as the tenth most common cancer to affect both genders. The latest statistics (National Cancer Registry 1999) reflect a sharp increase in this cancer, now ranked as the fifth most common cancer in males and third most common in females (Mqoqi et al 2004).

2.2.1 ETIOLOGY OF COLORECTAL CANCER

Cancer develops as a result of mutations accumulating over time, in genes which normally function to facilitate proper cell growth and differentiation

(Vogelstein and Kinzler 1993). In 80% of individuals, CRC results as a sporadic disease with no evidence of an inherited predisposition whereby environmental and dietary factors play a key role (Lalloo et al 2005; Schulmann et al 2002). Several prospective studies have linked a typical westernised diet associated with an increased consumption of red meat and saturated fat, alcohol and cigarette smoking to a greater risk of developing colorectal malignancies (Giovannucci et al 1992; Willett et al 1990). Conversely, low consumption of red meat, dietary fat and a high consumption of folate, vegetables and fibre suggest a protective effect. Recent data from observational studies and negative results from randomised trials, however, contradict the association between fibre and CRC risk (Campos et al 2005; Michels et al 2005; Tsubono et al 2005).

Migrant studies provide further evidence of the role of environmental and dietary influences in the development of CRC. These studies have reported an increase in incidence of CRC when immigration occurs from a low-risk to a high-risk country (Kolonel et al 1980; McMichael et al 1980). This phenomenon is also illustrated in individuals relocating from high- to low-risk areas (McMichael et al 1980). Interestingly, the study found that amongst these immigrants the incidence of CRC was shown to decrease to those of the host country within only one generation. Walker and Segal (2002) propose similar trends in the Black SA population, where a rising occurrence of CRC has been reported specifically in the urban population as compared to their rural counterparts. In the Utah population (USA), CRC risk was also significantly different when Mormons were compared to non-Mormons. The Mormons generally have strong proscriptions against the use of certain dietary components (meat, sugar, cheese, alcohol and tobacco), some of which have an association with cancer risk (Jorde 2001; National Research Council 1982).

The risk of developing CRC increases with the number of affected relatives and a decreasing age of diagnosis (Lalloo et al 2005). For the remaining 20%

of patients who do not fall within the sporadic CRC group, familial CRC is apparent and the underlying predisposition, attributed to an inherited susceptibility to disease. LS, the most common of the inherited CRC's, accounts conservatively, for approximately 20-35% of such cancers (Figure 3) (Lynch and Krush 1971; Warthin 1913).

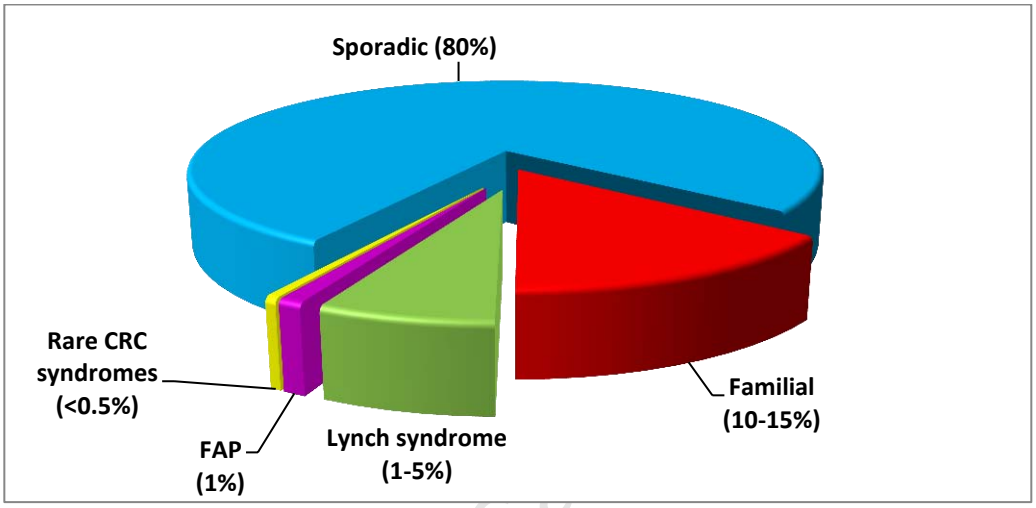

Figure 3: Contribution of Lynch syndrome to the colorectal cancer burden (Lynch and de la Chapelle 2003; Lynch and Lynch 2000; Lynch and Krush 1971).

2.3 OVERVIEW OF LYNCH SYNDROME (LS)

Historically, the first report of LS was described by Aldred Warthin in 1985. The pathologist's observation of an hereditary nature of cancer was initiated by his seamstress's anxiety concerning her family history of malignancy and her fears of mortality in light of the proclivity towards cancers in her family (Warthin et al 1913). The pedigree of this family, now known as Family G, was published by Warthin in 1913 and similar families presenting with an analogous constellation of cancers were subsequently described under the appellation of 'Cancer Family Syndrome' (CFS) (Lynch et al 1966; Lynch and Krush 1971).

Following the recognition of an autosomal dominant mode of inheritance of CRC, CFS became better known as LS (Douglas et al 2005; Lynch and Smyrk 1996; Vasen and Morreau 2002). To differentiate families where

extracolonic cancers were additionally apparent, LS I and LS II were delineated (Mecklin et al 1986; Vasen et al 1989). Families with early onset CRC were grouped into the first category, while those cases with a litany of integral cancers in addition to CRC became known as LS II (Lynch and Lynch 2000). A series of international publications documented the existence of families with LS in Europe (Itoh et al 1990; Mecklin et al 1986; Ponz de Leon et al 1989; Vasen et al 1989), New Zealand (Jass et al 1992) and Israel (Abusamra et al 1987). Following this global recognition the more descriptive acronym, Hereditary Nonpolyposis Colorectal Cancer (HNPCC), came into use. The term was chosen to place emphasis on the hereditary nature of the condition and to differentiate it from the polyposis syndromes. Presently, a new definition favours the use of LS for genetically proven cases of the condition (with molecular evidence of a mismatch repair defect) (Boland 2005; Lindor et al 2006; Lynch et al 2009; Vasen et al 2007).

To prevent any confusion in this research project, the condition will hereforth be referred to as LS. However, should LS only be suspected on a clinical basis, without proof of a genetic confirmation, it will clearly be indicated in the review.

2.4 MOLECULAR BASIS OF LYNCH SYNDROME

LS is an autosomal dominant condition caused by mutations in DNA mismatch repair (MMR) genes causing multiple generations within the family to be affected with CRC (Lynch and de la Chapelle 2003). The discovery of the genetic basis for LS began with Peltomäki et al (1993) linking the cancer-susceptibility locus to chromosome 2p. A second predisposing locus, on chromosome 3p, was described by Lindblom et al (1993) shortly afterwards. Currently four genes have been implicated in the MMR pathway and are known to be associated with LS. These include MLH1, MSH2, MSH6 and PMS2 (Abdel-Rahman et al 2006; Lynch et al 1998; Vasen and Morreau 2002).

MMR genes function to maintain the fidelity of the DNA by repairing errors of DNA replication created by misincorporations or slippage of the DNA-polymerase (Annie Yu et al 2003). MMR mutations associated with LS are described and maintained by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) (INSIGHT 2008).

The proportion of LS families due to mutations within each gene remains to be elucidated. Data thus far has suggested that MLH1 and MSH2 account for the majority of cases (90%) followed by MSH6 (7-10%), with PMS2 fewer than 5% (Berends et al 2002; Miyaki et al 1997; Peltomäki et al 2003).

2.5 CLINICAL FEATURES OF LYNCH SYNDROME

Individuals with a predisposing mutation have an approximate 70-80% lifetime risk of developing CRC at an early age (mean of approximately 45 years) with a predilection to right-sided tumours (Mecklin 1987; Rodriquez-Bigas et al 1997; Lynch et al 1993b). This is in contrast to sporadic CRC which occurs later in life, at approximately 65 years, and usually shows predominance for the left colon (Annie Yu et al 2003; Lynch et al 1998; Vasen et al 1999; Watson et al 1998). Typical colonic features of LS include the excess of synchronous (multiple tumours seen at or within six months of surgical resection for CRC) and metachronous (tumours occurring more than six months after surgery) tumours (Lynch and de la Chapelle 1999). Additionally, LS patients present with a paucity of adenomatous colonic polyps, whereby the precursor lesions are often more villous, with areas of high-grade dysplasia, than those from the general population with sporadic CRC. Consequently a more rapid adenoma to carcinoma progression occurs during malignant transformation in LS (Annie Yu et al 2003; Jass and Stewart 1992; Lynch and Lynch 2000). Greater detail, with respect to the clinical features of LS, is provided in Table 1.

Table 1: The characteristics which typify Lynch syndrome.

- **Autosomal dominant inheritance pattern present in the family pedigree**
- **Earlier average age of onset as compared to the general population**
    - 45 years in LS versus 69 years in the general population (Vasen et al 1999)
- **Predilection for proximal (right-sided) CRC**
    - Approximately 70% of cases develop proximal to the splenic flexure (Annie Yu et al 2003)
- **Accelerated carcinogenesis**
    - Carcinomas develop within 2-3 years in LS versus 8-10 years in the general population (Jass and Stewart 1992; Lynch and de la Chapelle 2003)
- **Increased risk for secondary CRCs**
    - 25-30% of patients develop a second CRC within 10 years of surgical resection (if surgery does not include a subtotal colectomy) (Barrow et al 2009; Watson et al 2008)
- **Increased malignancy risk for extracolonic tumours**
- **Endometrium, ovary, stomach, small bowel, hepatobiliary tract, pancreas, ureter and renal pelvis, brain (Turcot syndrome variant of LS), skin including sebaceous adenomas, carcinomas and keratoacanthomas (Muir-Torre syndrome variant of LS)**
- **Typical pathology: poorly differentiated carcinomas with an excess of mucoid and signet-cell features, Crohn's-like reaction and tumour infiltrating lymphocytes within the tumour**
- **Increased survival as compared to sporadic CRC**
    - A relative survival rate of 65% in LS patients compared to 44% in sporadic CRC cases (Sankila et al 1996)
- **The diagnosis of a germline mutation within MLH1, MSH2, MSH6 or PMS2**

Malignancy associated with LS is not only limited to the colon. Individuals are at risk of a variety of other extracolonic cancers, namely, endometrial cancer in females (Watson et al 1994). The trait is additionally associated with an increased lifetime risk of gastric cancer (particularly in Asian countries such as Japan and Korea), urinary and biliary tract adenocarcinomas (Aarnio et al 1995; Aarnio et al 1999; Barrow et al 2009; Park et al 2000). An excess of pancreas, larynx, brain and hematopoietic cancers has also been described (Lynch et al 1993a). Defining breast cancer as one of the LS tumours remains

controversial and the debate, in this regard, is ongoing. Vasen et al (2001a) did not show breast cancer to be part of the spectrum; however Barrow et al (2009), Blokhuis et al (2008) and Scott et al (2001) did prove the incidence to be higher than the population risk.

2.5.1. GENDER DIFFERENCES

Gender has been suggested to modify tumour expression in LS. In a Scottish study involving 67 patients who harboured mutations in MMR genes, the risk of developing CRC to age 70 was significantly higher for males as compared to females (p=0.006). CRC manifested in 74% of males compared to only 30% of females. Interestingly, the risk for uterine cancer considerably exceeded the lifetime risk for CRC in females from this cohort (42% versus 30%) (Dunlop et al 1997). The latest literature suggests similar gender differences with respect to the expression of the LS phenotype in females (Aarnio et al 1999; Hampel et al 2005b).

2.5.2 GENOTYPE-PHENOTYPE

The existence of genotype-phenotype correlations are gaining clarity. In a recent study, an American group determined the prevalence of cancer in 1914 unrelated probands with an identified germline mutation. The results described a marked discrepancy between cancer prevalence when different gene mutations were considered. While the endometrial cancer risk was similar between MLH1 and MSH2 mutation carriers, MLH1 carriers had a ten percent higher risk for CRC than individuals with an MSH2 mutation. Additionally, the mean age of CRC was younger for MLH1 mutation carriers (42.2 versus 44.8 years) (Kastrinos et al 2008).

2.5.3 HISTOPATHOLOGY

No robust biomarkers exist for LS. The pathological features of CRC are often distinguishable, but not entirely predictive of all cases of inherited CRC. The histopathology of LS CRC‘s tend to be poorly differentiated, abundant in

extracellular mucin and illustrate a lymphoid (Crohn's-like pattern or peritumoural lymphocytes) host response to the tumour (Smyrk et al 1990) or signet cell pathology (Jass et al 2007). The most useful biomarker has been microsatellite instability (MSI), which is further described under Section 2.6.3.

2.6 DIAGNOSTIC CRITERIA

The recognition of LS is not straightforward and diagnostic criteria continue to evolve as the understanding and characterisation of the disorder improves. Currently, the diagnosis of LS is made on the basis of clinical Amsterdam criteria or molecular diagnosis by testing for germline mutations in one of the MMR genes.

2.6.1 AMSTERDAM CRITERIA

The Amsterdam criteria were established to define LS on the basis of a clinical history (Table 2A).

Table 2A: Amsterdam criteria I.

AMSTERDAM CRITERIA I (Vasen et al 1991)
At least three relatives affected with histologically verified CRC: • One of the affected should be a first-degree relative of the other two affected individuals; • At least one of the CRC cases should be identified before the age of 50 years; • FAP should be excluded; • Tumours should be verified by pathology [a].

[a]All the preceding criteria need to be present. CRC-Colorectal cancer.

These criteria, created in 1990 by the ICG-HNPCC, were developed for the purpose of standardising diagnostic criteria in the recruitment of suspected cases of LS patients for collaborative studies (Vasen et al 1991). Essentially the guidelines stipulate that the family history must represent one or more CRC's diagnosed before 50 years of age and at least three relatives with CRC in two generations, where one must be a first-degree relative of the other two (Strate and Syngal 2005; Vasen et al 1991). Importantly, the

Amsterdam criteria do not account for patients from small families or with other LS-related cancers. In response to this criticism, the Amsterdam II criteria were developed in 1999 to be more inclusive of extracolonic cancers and the Modified Amsterdam criteria was developed for assessing smaller families (Bellacosa et al 1996; Vasen et al 1999) (Table 2B).

Table 2B: Amsterdam criteria II.

AMSERDAM CRITERIA II (Vasen et al 1999)
At least three affected relatives should be affected with LS-related cancer, including CRC, cancer of the endometrium, stomach, small bowel, ovary, ureter (renal pelvis), brain, hepatobiliary tract and skin (sebaceous tumours): • One of the affected individuals should be a first-degree relative of the other two affected individuals; • At least two successive generations should include affected family members; • At least one of the syndrome associated cancers should be diagnosed before the age of 50 years[a]; • FAP should be excluded; • Tumours should be verified by pathology[b].

[a]The syndrome associated tumour spectrum includes: CRC, endometrial, stomach, small bowel, ovarian, pancreas, ureter (renal pelvis), biliary tract, brain (Turcot syndrome), sebaceous gland adenomas and keratoacanthomas (Muir-Torre syndrome).
[b]All the preceding criteria need to be present.
CRC-Colorectal cancer.

The accuracy of the clinical criteria (Amsterdam I and II and modified Amsterdam) strongly depends on the accuracy of the reported family history and Katballe et al (2001) suggested that this could be further enhanced by verifying diagnoses with pathology reports. When considering the original Amsterdam criteria, the sensitivity and specificity for identifying a mutation in MLH1 and MSH2 has been documented at 61% and 67% respectively. This can be increased to 72% and 78% when the modified and Amsterdam II criteria are used (Syngal et al 2000). Importantly, when Syngal et al (2000) classified the accuracy of existing clinical criteria, they found that up to 39% of families with a germline MMR mutation did not meet the Amsterdam criteria and concluded that the Amsterdam guidelines should not be the sole criterion for determining which families should undergo genetic testing for mutations in MLH1 and MSH2.

2.6.2 BETHESDA GUIDELINES

The Bethesda criteria were drafted to guide decisions for determining which tumours should undergo genetic testing (Table 2C). These guidelines included Amsterdam criteria as well as further pathological evaluation, allowing for a less stringent assessment. Original guidelines were proposed in 1996 and subsequently revised in 2002 following further developments in the field (Umar et al 2004).

Table 2C: Revised Bethesda Guidelines for testing of colorectal tumours for microsatellite instability.

BETHESDA GUIDELINES (Laghi et al 2004)
Tumours from any of the following should be tested for microsatellite instability and then proceed to molecular analysis if positive:
• CRC diagnosed in a patient under the age of 50 years; • Presence of synchronous or metachronous CRC or any other syndrome related tumour[s] regardless of age; • CRC with microsatellite instability-high[b] histology[c] in a patient who is less than 60 years of age; • CRC or a syndrome-related tumour diagnosed under the age of 50 years in at least one first-degree relative; • CRC or a syndrome-related tumour diagnosed at any age but present in two first or second degree-relatives.

[a]The syndrome associated tumour spectrum includes: CRC, endometrial, stomach, small bowel, ovarian, pancreas, ureter (renal pelvis), biliary tract, brain (Turcot syndrome), sebaceous gland adenomas and keratoacanthomas (Muir-Torre syndrome).
[b]MSI-H tumours are associated with changes in two or more of the five microsatellite markers.
[c]Presence of tumour infiltrating lymphocytes, Crohn disease-like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern.
CRC-Colorectal cancer.

The revised Bethesda criteria, recommend MSI and or immunohistochemistry (IHC) prior to starting with mutation analysis. The fulfilment of only one guideline is sufficient for MSI and or IHC testing to be performed and acts as a screening tool to identify which patients are most likely to have a MMR mutation.

2.6.3 MICROSATELLITE INSTABILITY (MSI)

Microsatellites are length variations of short repetitive DNA sequences which are particularly susceptible to acquiring somatic mutations when the MMR gene function is impaired (Vasen and Morreau 2002). Cancer arising in a cell with a flawed MMR system will exhibit an inconsistent number of microsatelillite repeats when compared to normal tissue, thereby manifesting microsatellite instability (MSI). Testing for MSI identifies tumour characteristics predictive of underlying MMR mutations.

The National Cancer Institute workshop on LS proposed that a panel of five markers be incorporated to assess MSI. These markers are microsatellites present in regions of the genome that are irrelevant to malignant transformation (Resnick et al 2009). Classification occurs according to three categories: MSI-high, defined as two or more markers showing instability; MSI-low, if one marker reflects instability; and MSI-stable where no markers show instability. The occurrence of MSI is higher in tumours of patients who are clinically diagnosed with LS (Aaltonen et al 1998; Boland et al 1998; Cunningham et al 2001), occurring in 85-92% of colorectal carcinomas and in at least 75% of endometrial carcinomas associated with LS (Aaltonen et al 1994). Significantly lower estimates occur in sporadic colorectal (10-15%) and endometrial (17%) carcinomas (de Leeu et al 2000; Thibodeau et al 1993). The general recommendation is to use MSI as a pre-screening tool, to determine which families are likely to benefit from mutation analysis as the process is labour intensive, expensive and time-consuming. Testing for the presence of promotor hypermethylation and/or a somatic mutation (V600E) in the *BRAF* gene is a strong indicator of a sporadic CRC, and combining these strategies can reduce costs associated with mutational analysis (Domingo et al 2004).

In addition to MSI‘s screening use, the test is also important as MSI-H tumours are associated with a better clinical prognosis, stage for stage and overall (Gryfe et al 2000). At the same time MSI also predicts a fairly poor

response to adjuvant chemotherapy for stage I and II tumours (Ribic et al 2003).

As stated earlier, MSI is sensitive, but not specific to LS as a germline mutation will only be identified in 20-25% of all MSI-H tumours. For this reason, IHC is of a complementary value.

2.6.4 IMMUNOHISTOCHEMISTRY (IHC)

IHC is used to determine if there is expression of the MMR gene protein product. IHC can be used in combination with MSI to fast-track the identification of the specific MMR gene underlying the germline mutation. IHC for MLH1, MSH2, MSH6 and PMS2 is commercially available and is approximately 95% sensitive in the identification of MMR protein deficiency. As a result of MMR interactions, ambiguous staining can take place and experience on the part of the pathologist interpreting the slides is a requisite (Lynch et al 2009). In a large study involving 818 unselected CRC cases, Lindor et al (2002) concluded that IHC was 100% specific and 92.3% sensitive. Vasen and Boland (2005) suggested that the selection of IHC versus MSI should be based on the probability of identifying a genetic mutation. IHC might be the more feasible first step in families meeting the Amsterdam criteria where a higher possibility of finding a MMR gene mutation exists. If normal IHC results are found, supplementary MSI may be conducted. The reversal might be considered in patients meeting Bethesda criteria but who fail to be included in the Amsterdam criteria. These findings were in contrast to Hampel et al (2005a) who argued that a combination of MSI and IHC detected all mutations (23/23), while genotyping with IHC alone (2/23 cases were missed) or MSI alone (similarly 2/23 missed) failed to identify two probands. In a more recent publication by the same author, IHC is regarded as an almost equally sensitive screening tool to MSI and the group motivate for IHC due to its ability to direct genetic testing to a specific gene (Hampel et al 2008).

2.6.5 RISK ASSESSMENT MODELS

Barnetson et al (2006) suggest that pre-screening still misses an appreciable amount of mutations in MMR genes and proposed a new two-step approach developed from a population-based study of unselected patients under the age of 55 years with CRC. From their study the authors were able to identify the most pertinent clinical features suggestive of an underlying MMR mutation. Their computer-based algorithm incorporates a scoring system based on clinical features, providing a quantitative prediction of the likelihood of finding a MMR mutation. A threshold can be selected when using the equation, thereby taking into account the preferences and resources of the centre conducting the testing. While the benefits of the resource are evident and superior to that of the Amsterdam and Bethesda criteria (at a 0.5% likelihood), the model has only been assessed on 73 patients with proven mutations and a replication set of 155 subjects. The replication set was recruited retrospectively and showed a much younger age of onset of CRC, compared to that of the patients on which the model was developed. A variety of other models exist (Leiden Model, MMRPro, PREMM Model), each with their own benefits and limitations.

2.6.6 MOLECULAR TESTING

Clinical genetic testing is available beyond the SA border for MLH1, MSH2 and MSH6 for approximately R8 000 to R22 000 (USA$ 1000-3000). The preferred laboratory techniques used to detect mutations predisposing to LS include mutation screening (detection rate of 60-69% in MLH1, 50-69% in MSH2) and sequence analysis (detection rate of 90-95% in MLH1, 50-80% in MSH2). Large deletions and rearrangements may be missed by these methods and a further 5-10% in MLH1 and 17-50% in MSH2 can be gained with the use of supplementary procedures such as Multiplex Ligation-Dependent Probe Amplification and Southern-blotting (Genereviews 2006). Screening of MSH6 rarely yields mutations as a minority of LS families are found to have pathogenic changes within this gene (Berends et al 2002).

Testing in SA is currently offered free-of-charge on a research basis in one laboratory in the Western Cape. Denaturing high–performance liquid chromatography analysis is used to screen for DNA variations in MLH1, MSH2 and MSH6, with subsequent direct-cycle sequencing performed to characterise detected variations. The 12 existing mutations (seven in MLH1 and five in MSH2) identified in the SA cohort through this research, are used to screen referrals of cases with suspected LS. At present, two private SA laboratories are in the process of setting up clinical genetic testing for LS.

2.7 EPIDEMIOLOGY OF LYNCH SYNDROME

The frequency of LS has been estimated to contribute to as much as 13% of the total CRC burden (Lynch and de la Chapelle 1999; Lynch and Smyrk 1996), however, most appraisals predict significantly lower frequencies of approximately one to six percent (Lynch and de la Chapelle 2003; Mecklin 1987; Mecklin and Ponz de Leon 1994). The disparity is largely due to the difficulty in diagnosing LS as a result of the variety of clinical phenotypes associated with the syndrome in different centres or countries (Bellacosa et al 1996; Rodriguez-Bigas et al 1997).

Initially the ICG-HNPCC defined clinical diagnostic criteria (Amsterdam criteria) for LS to promote uniformity in collaborative studies (Vasen et al 1991). Several study groups have estimated Amsterdam-defined LS. Mecklin et al (1995) estimated the proportion of clinically suspected cases of LS in 406 CRC cases to be 0.7% in a prospective multicentre study from ten hospitals in Finland. Evans et al (1997) reported a frequency of 0.3% in their analysis of 1137 English registry patients, while the Danish group found three cases out of 1328 (0.3%) fulfilled the Amsterdam criteria (Katballe et al 2002).

Not only does the estimated frequency of LS fluctuate according to different countries, geographic variations in the frequency of LS also exist. Modica et al (1995) and Ponz de Leon et al (1999), for example, showed that incidence rates are appreciably higher in the Northern than the Southern Italian regions.

Ponz de Leon et al (1993) reported that Amsterdam-defined cases of LS occurred in 3.4% of CRC cases in Northern Italy as opposed to a prevalence of 0.45% in Southern Italy. The population studied by Cornaggia et al (2000), who drew on information from the Lombardy Cancer Registry, demonstrated a much lower frequency in their study (0.5%) compared to other areas in Italy.

The disparities among population groups may reflect actual population differences. However, it has been suggested that variations may be further compounded by differences in the ability to verify diagnoses among family members and the level of proof required by each study to verify the diagnosis, as pertains to the Amsterdam criteria (Katballe et al 2002; Wang et al 2007). Another approach to diagnosing LS has focused on screening for germline mutations in MMR genes predisposing to LS, primarily MLH1 and MSH2. A Finnish group estimated the frequency of LS, based on 535 consecutive CRC patients tested for MLH1 and MSH2 germline mutations, to be 3.4% (Salovaara et al 2000). The current trend in similar studies conducted in China (Wang et al 2007), the Baltic States (Irmejs et al 2007) and USA (Samowitz et al 2001) is to use less strict criteria when selecting patients for molecular analysis, as mutations have been found in cases of suspected LS where the proband did not meet the Amsterdam criteria (Aaltonen et al 1998; Ravnik-Glavik et al 2000; Tanyi 2009).

Thus discordant results are not only likely to reflect population differences, but additionally the varied methodologies used to extrapolate the frequency of LS among CRC cases (Irmejs et al 2007; Samowitz et al 2001). While studies are currently indicating lower incidences of LS than previously thought, it remains clear that the Amsterdam criteria are stringent and the rigid application thereof, as it is used to define suspected cases of LS, may lead to many missed classifications of CRC as LS-related. A similar proclamation can be made for figures derived from studies utilising screening analysis to diagnose LS, as only two of the known five causative genes predisposing to LS have been screened in most of the reported studies (Wang et al 2007).

Taking this into consideration, it is possible that future research studies may point to LS contributing to a greater proportion of all CRC malignancies.

Table 3 lists all the published incidence figures for LS. The incidence percentage is given in accordance with the methodology used, either defined by an entry under ‗Amsterdam criteria or mutational analysis', or two entries if both methods were used to ascertain the reported frequency of LS. The region where the study was conducted and the sample size of the study are included.

Table 3: Incidence of Lynch syndrome by geographical region.

Country	No. of index cases	Amsterdam Criteria	Mutation screening of MLH1 and MSH2†	Description of study (design and method)	Published reference
		ASIA			
China	1988	5.7%	1.3%	Prospective; consecutive patients from a single institution; four year recruitment	Wang et al 2007
		EUROPE			
Denmark	1200	1.5%	1.7%	Prospective; multicentre study on consecutive CRC patients; four year recruitment	Katballe et al 2002
England	1137	0.3%		Retrospective and prospective; review of all CRC cases from one institution; recruited over 14 years	Evans et al 1997
Finland	509		2%	Prospective; consecutive patients from nine hospitals; two year study	Aaltonen et al 1998
Finland	535		3.4%	Retrospective and prospective multicentre of all recruited CRC patients; collection phase of two years	Salovaara et al 2000
Finland	406	0.7%		Prospective; multicentre study of CRC patients; one year recruitment phase	Mecklin et al 1995
Hungary	809	6%	1.7%	Retrospective and prospective; single institution recruitment of patients; collection phase spanning nine years	Tanyi 2009
Ireland	1241	1-2.6%		Retrospective; review of CRC cases over three year study period	Kee and Collins 1991
Italy	485	1%		Prospective; multicentre study on consecutive CRC patients (collection period not indicated)	Riegler et al 1999
Italy	817	3.4%		Retrospective; review of cancer registry over six year period	Ponz de Leon et al 1993
Italy	197	0.5%		Retrospective; review of cancer registry (collection period not indicated)	Cornaggia et al 2000
Italy	1721	2.6%		Retrospective; review of cancer registry over 12 years	Ponz de Leon et al 1999
Italy	389	4.3%		Retrospective; review of two cancer registries over three years	Modica et al 1995
Italy	213	0.46%		Retrospective; review of two cancer registries over three years	Modica et al 1995

†MSI analysis and subsequent mutation screening in MLH1 and MSH2. CRC-Colorectal cancer.

Table 3: Incidence of Lynch syndrome by geographical region (continued).

Country	No. of index cases	Amsterdam Criteria	Mutation screening of MLH1 and MSH2†	Description of study (design and method)	Published reference
		Europe			
Latvia	702	0.14%	1%	Prospective; multicentre study on consecutive patients; recruitment over four years	Irmejs et al 2007
Poland	170	2.4%		Prospective; CRC surgical patients seen in a single centre; recruited over three years	Jawien and Banaszkiewicz 1998
Slovenia	300		1%	Prospective; multicentre study conducted over a two year period	Ravnik-Glavac et al 2000
		Australia			
Australia/ North America	8369	9.5%		Prospective; CRC Registry of six centres over 10 year period	Newcomb et al 2007
Australia	786		0.8%	Prospective; CRC patients from one institution (collection period not indicated)	Ward et al 2005
		North America			
Israel/New York	686		0.69%	Retrospective; multicentre collaborative study of Ashkenazi Jews (screening for a common founder mutation only in MSH2- collection period not indicated)	Foulkes et al 2002
USA	1134	0.9%		Prospective; Multicentre study over three year period	Peel et al 2000
USA	257		1.9%	Prospective; Unselected patients referred for CRC resection over one and a half year period	Cunningham et al 2001
USA	1066		0.86%	Retrospective; multicentre study over three year period	Samowitz et al 2001
USA	1066		2.2%	Retrospective; CRC patients recruited over 15 years	Hampel et al 2005a
USA	1566		2.8%	Prospective; CRC patients from six institutions seen over a five year period	Hampel et al 2008

†MSI analysis and subsequent mutation screening in MLH1 and MSH2. CRC-Colorectal cancer.

2.7.1 FOUNDER MUTATIONS

Mutations that occur at high frequencies within a specific population group may be *de nova* or ancestral (founder effect) in nature. The two can be relatively easily distinguished from one another through haplotype analysis. Founder mutations occur on the same haplotype while recurrent *de nova* mutations do not. A founder mutation results in an unusually high frequency of a particular allele or haplotype in a population, implying that all the individuals with the sequence descended from the same ancestors (Turnpenny et al 2005). Typically, founder effects occur following rapidly growing populations from a small number of founders, with or without the influence of influx of people from different origins (Lynch and de la Chapelle 1999). Another mechanism for this effect is through the expansion of populations following a bottleneck (reducing the population to a smaller number), whereby the mutation becomes more prevalent in a larger proportion of the population, namely, through gene enrichment (Read and Donnai 2009).

Founder mutations have generated considerable interest in molecular genetic studies as screening in a population known to have a founder mutation, can facilitate targeted testing to the mutation, allowing for a more rapid and less expensive test (Lynch et al 2009; Neuhausen 2000; Zeegers et al 2004). Reports on founder mutations predisposing to cancer have only recently emerged. The best-known recurrent mutation predisposing to LS is the A to T transversion in intron 5 of MSH2. The mutation accounts for up to 10% of all cases of LS and has been reported worldwide (Desai et al 2000; Froggat et al 1999; Hampel 2005a; Liu et al 1994).

Moisio et al (1996) identified the ‗Finland 1' mutation which involves a deletion of exon 16 on MLH1. The mutation was identified in 40 unrelated families in Sweden and Finland. Genealogical evidence has shown that the majority of affected individuals with the mutation were descendants of a common founder of this Finnish subpopulation, with the mutation likely to date back over a

thousand years (Moisio et al 1996; Nyström-Lahti et al 1994). Interestingly, the founder mutation was identified in over two thirds of LS diagnoses in a Finnish study determining incidence among 509 consecutive CRC patients (Aaltonen et al 1998; Mecklin et al 1995; Nyström-Lahti et al 1994).

In a more recent study, Foulkes et al (2002) reported on a founder mutation in MSH2 to be highly enriched in their study of 15 families of Ashkenazi Jewish descent. The genetic change, a substitution of proline for alanine, accounts for approximately 20% of LS cases among the diaspora of Ashkenazi Jews from Europe. The estimated age of the mutation is in the range of 200-500 years.

In SA, a common, A to T transversion in exon 13 of MLH1, has been described (Ramesar et al 2000). The mutation has only been observed in families of Mixed Ancestry in SA and has not been reported in any other populations as verified by the human genome mutation database (HGMD 2008). Research, involving haplotype analysis, has confirmed that this mutation spread along the west coast of SA as a result of a founder effect (Savanhu et al 2005). Founder mutations have additionally been described for the Northern American (Wagner et al 2003), Italian (Caluseriu et al 2004; Lastella et al 2011; Stella et al 2007; Thiffault et al 2004) and Chinese populations (Chan et al 2004).

2.8 CANCER SPECTRUM AND SURVEILLANCE

Surveillance in LS is largely influenced by the efficacy of a particular prevention strategy and the estimates of cancer risk associated with LS. As recommendations are principally based on studies that are retrospective in nature, considerable weighting to such recommendations has been recommended by panels of experts (Vasen et al 2007). For screening to be routinely offered and recommended, the following should be taken into consideration: (1) the tumour should be fairly common; (2) the tumour should

be treatable if detected early; (3) the outcome should be serious if the tumour is advanced, while being treatable if detected early; (4) accurate detection methods for pre-malignant tumours should exist (Lambert 1983).

2.8.1 COLORECTAL CANCER

CRC is the most common tumour type occurring in individuals with mutations in MMR genes, accounting for between 53-94% and 63-96% lifetime CRC risk with MLH1 and MSH2 mutations respectively (Aarnio et al 1999; Barrow et al 2008; Lin et al 1998; Stupart et al 2009a; Voskuil et al 1997). MSH6 mutation carriers present with a lower incidence of CRC and a later age of onset (Plaschke et al 2004). Several studies have suggested higher CRC risk in males as compared to females (Dunlop et al 1997; Hendriks et al 2004). For both genders, CRC risk is much higher than the risk in the general population and warrants the same intensive screening in females as in males (Watson and Lynch 2001).

Full colonoscopy is mandatory in MMR gene mutation carriers as tumour distribution is predominantly right-sided (Järvinen et al 2000; Stupart et al 2009a). Regular surveillance is recommended as the adenoma-carcinoma sequence is accelerated in individuals with LS (Natarajan et al 2010; Stormorken et al 2007; de Jong et al 2004). The precursor lesion, adenoma, may develop into a carcinoma within two to three years as opposed to eight to ten years in sporadic CRC (Jass and Stewart 1992; Lynch and de la Chapelle 1999). Current guidelines propose surveillance of the colon to be initiated at the age of 20-25 years, or ten years prior to the onset in the youngest affected family member, and should be repeated every one to three years (Vasen et al 1991; Vasen et al 1999).The longer interval (two yearly) during the first decade of screening relates to the low risk of CRC before the age of 30 years (Barrow et al 2009; Hampel et al 2005a; Hendriks et al 2004; Plashchke et al 2004; Quehenberger et al 2005). Guidelines relating to the upper age limit of screening are scarce within the literature. De Jong et al (2006) found that the risk of developing CRC after the age of 80 years, in their

cohort of mutation carriers, was low relative to their life expectancy. In SA, screening is recommended every two years until 30 years of age and annually thereafter (Goldberg et al 1998). Currently, international studies are following this trend and advocating more intensive surveillance (Engel et al 2010; Vasen et al 2010).

A clinical trial extending over 15 years evaluated the efficacy of regular colonoscopic surveillance in families with LS (Järvinen et al 1995). The study established that screening for CRC, on a three yearly basis, halved the risk of CRC and decreased mortality by 65% in such families. In a later study by the same Finnish group, surveillance outcomes of 56 families were assessed. Twenty-one cancers were identified following a _clean colonoscopy', with half of the cancers presenting within the three year interval period (Järvinen et al 2000). Optimal screening currently lies between one and two years and is largely dependant on the centre offering surveillance.

The risk of a second colonic tumour has been reported to be as high as 16% in an individual with LS (de Vos tot Nederveen Cappel et al 2002). Preferred treatment is thus to offer a subtotal colectomy with ilieorectal anastomosis as the primary surgical intervention and not segmental resection (Natarajan et al 2010; Stupart et al 2010; Vasen et al 2007; Vasen and de Vos tot Nederveen Cappel 2011). Unfortunately, due to the small risk of a rectal carcinoma, lifelong endoscopic surveillance of the rectum is still recommended following surgical removal of the large bowel (Nataranjan et al 2010; Stupart et al 2010). The debate of whether or not prophylactic subtotal colectomy should routinely be considered is ongoing. Surprisingly, a Finnish study evaluating surveillance outcome among 242 mutation-positive individuals identified that only 1.2% of their participants, had opted for prophylactic colectomy over the ten-year period of their study (Järvinen et al 2009).

2.8.2 ENDOMETRIAL CANCER

The cumulative lifetime risk for women with LS ranges from 19-71% as opposed to 3% in the general population (Aarnio et al 1995; Dunlop et al 1997; Hendriks et al 2004; Lin et al 1998, Vasen et al 2007). Interestingly, the lifetime risk of endometrial cancer often exceeds the CRC risk for women predisposed to LS (Hampel et al 2005b). Risks conferred by MLH1 and MSH2 are lower than MSH6 mutation carriers. In a recent study by Barrow and co-workers (2009), 121 LS families were assessed for the cumulative lifetime risk of endometrial cancer. Their study demonstrated a significant risk for all three gene mutations, specifically MSH6 which predisposed to a 48.8% lifetime risk at age 70 years. Hendriks et al (2004) also found that women with an MSH6 mutation have a more than two-fold greater risk of endometrial cancer when compared to their MLH1 and MSH2 counterparts. In an earlier study by Goodfellow et al (2003) the prevalence of MSH6 mutations in an unselected endometrial cancer cohort, showed that seven of 441 endometrial cancers were as a result of an MSH6 mutation. They suggested that mutations in MSH6 were relatively common in endometrial cancer patients.

The average age of onset of an endometrial cancer in LS is approximately 50 years, ten years earlier than that of a sporadic endometrial cancer (Aarnio et al 1999; Dunlop et al 1997). Regular surveillance of the endometrium is not currently performed in the general population due to the low prevalence of the disease. As a result information on the sensitivity and specificity of this screening is limited.

Screening modalities that have been suggested for women with LS include transvaginal ultrasound (TVU) and intrauterine biopsies of the endometrium. A collaborative study involving British and Dutch investigators evaluated the outcome of transvaginal surveillance in 269 women from suspected LS families. Ultrasound was performed on a one- to two-yearly basis. No premalignant lesions or endometrial cancers were detected. Unfortunately, two interval cancers did develop following a normal ultrasound investigation,

suggesting this method may not effectively detect early endometrial carcinoma (Dove-Edwin et al 2002). Renkonen-Sinisalo et al (2007) assessed gynaecological surveillance consisting of TVU and intrauterine biopsies of the endometrium in 175 women with LS. Remarkably, of the 14 endometrial cancers that were diagnosed, 11 were detected as a result of surveillance. Furthermore, if aspiration biopsy had not been introduced in addition to TVU, six of the 11 identified cancers would have escaped detection. Although evidence relating to the effectiveness of endometrial surveillance is limited, TVU and endometrial sampling is recommended from the age of 30-35 years.

As a result of the high risk of endometrial cancers, specifically in MSH6 mutation carriers, hysterectomy may be suggested as a prophylactic option following menopause. It has also been considered as an option for carriers of MLH1 and MSH2 mutations requiring surgery for CRC (Vasen et al 2007).

2.8.3 OVARIAN CANCER

Data on ovarian surveillance is meagre as most research studies have focused on the endometrial component when determining gynaecological surveillance. However, screening has not been effective in Hereditary Breast and Ovarian Cancer (HBOC) families, which confer high risks for inherited ovarian cancer (Van der Velde 2009). Screening for ovarian cancer in LS is, therefore, not a recommended guideline. Furthermore in the study by Renkonen-Sinisalo et al (2007), four ovarian cancers were undetected by TVU.

It has been suggested that women requiring CRC surgery should be given the option of a prophylactic hysterectomy. However, bilateral salpingo-oophorectomy could also be considered to eliminate the ovarian cancer risk. Two studies have confirmed the efficacy of prophylactic surgery. Schmeler et al (2006) assessed the outcome of 315 women with LS over a ten-year period. Individuals were grouped into two categories, control group (patients without prophylactic surgery) and patients with prophylactic surgery

(hysterectomy and bilateral salpingo-oophorectomy). Endometrial cancer was identified in 33% and ovarian cancer in 5% of the control group, whereas no gynaecological cancers were found in the group who had prophylactic surgery. These findings were later substantiated by Chen et al (2007), who confirmed the efficacy in their study.

2.8.4 BREAST CANCER

The general population's risk of developing breast cancer is high with a 1 in 10 lifetime risk (Lalloo et al 2005). In SA, breast cancer follows similar statistics to western countries and is the most common cancer to affect women (Sitas et al 1998; Vorobiof et al 2001). The inclusion of breast cancer into the LS spectrum remains controversial. Many authors report a low risk of breast cancer (Aarnio et al 1999; Dunlop et al 1997; Parc et al 2003; Vasen et al 2001; Watson et al 2008). Geary and co-workers (2008) identified 37 cases of breast cancer in their study involving 723 patients with LS. Their results showed that the calculated breast cancer risk was only slightly elevated and did not suggest a clustering in families or a younger age at diagnosis. Barrow et al (2009) reported MLH1 mutation carriers to have double the population risk, while the risk in MSH2 carriers was low.

Few studies have confirmed the involvement of the defective MMR gene when considering the breast cancer risk in LS. Blokhuis et al (2008) incorporated IHC and MSI testing on breast tumours identified in their study sample of LS patients in SA. The involvement of the MLH1 gene was identified in five of the seven cases that were tested. The seven cases occurred at a young age (mean of 46.3 years) and two were bilateral. Two smaller studies (Risinger et al 1996; Westenend et al 2005) and a more recent study (Walsh et al 2010) have also provided evidence of the involvement of MMR genes and motivate for breast cancer to be recognised as an integral tumour in patients with LS.

Watson et al (2008) argue against screening above the population-based protocols for breast cancer in individuals with LS. This argument has also been supported by Barrow et al (2009). In contrast, Blokhuis et al (2008) encouraged regular breast cancer surveillance in individuals with the common SA MLH1 C1528T mutation. The incidence of breast cancer in their study, while not reaching statistical significance, did illustrate MLH1 involvement in breast tumour development, accounted for the majority of extracolonic cancers (53%) and illustrated features of genetic predisposition (young age of onset and bilateral cases). The only other study conducted on this aspect in SA discouraged routine gynaecological surveillance (Stupart et al 2009a). While the authors also identified breast cancer to be the most common of the extracolonic malignancies in their cohort of 200 MLH1 mutation-positive individuals with the same MLH1 mutation, only 6% of females in their cohort developed breast cancer. They therefore support current policies of not offering routine gynaecological screening or prophylactic surgery to females with the common SA mutation.

2.8.5 GASTRIC CANCER

Gastric cancer is the second most frequent extracolonic cancer observed in individuals with LS (Vasen et al 1990). The majority of gastric cancers within the general population occur over the age of 55 years. Geary et al (2008) demonstrated that 79% of putatative mutation carriers with gastric cancer were diagnosed below the age of 55 years. There is a remarkable variability of the lifetime gastric cancer risk in individuals within different population groups. The associated lifetime risk of gastric cancer in the Netherlands is 2.1% (Vasen et al 2001b), 11-13% in the Finnish population (Aarnio et al 1997; Aarnio et al 1999) and has been predicted to approach 30% within the Korean population (Park et al 2000). Contrary to previous reports, gastric cancer seems to be more frequent than endometrial cancer in the Chinese population (Cai et al 2003). Environmental factors, such as the prevalence of *Helicobacter pylori* infection are likely to accelerate the development of gastric cancer in individuals with MMR mutations, accounting for the higher risk within endemic areas such as Korea (Park et al 2000). There has been some

suggestion that the gastric cancer risk is higher in carriers of an MSH2 mutation when compared to MLH1 (Aarnio et al 1999; Geary et al 2008; Lin et al 1998).

Surveillance for gastric cancer is questionable and evidence for regular screening in all at-risk individuals is insufficient to justify such an approach (Koornstra et al 2009). Upper gastrointestinal endoscopy may be recommended if more than one family member has developed gastric cancer or in countries with a high prevalence of gastric cancer (Park et al 2000; Vasen et al 2007).

2.8.6 SMALL BOWEL CANCER

The lifetime risk of small bowel cancer (SBC) has been reported to range from 1% to 4.2%, which is 100 times greater than the general population's risk for SBC (Aarnio et al 1995; ten Kate et al 2007; Vasen et al 1996; Watson et al 2008). Furthermore, Schulmann et al (2005) proclaim that SBC may be the first tumour manifestation in 50% of patients with suspected LS.

One of the initial studies on the characteristics of SBC, by Rodriguez-Bigas et al (1998), reported SBC in 42 individuals from LS families. The majority were classified as LS as a result of fulfilling the Amsterdam criteria and 15 of the 42 patients had a MMR mutation. Their study was based on mailed questionnaires to the ICG-HNPCC, sourcing information from registries in Australia, Canada, Denmark, Finland, Israel, Italy, Portugal, Netherlands and the USA. Forty-nine cases of SBC were identified in the 42 patients (more than one cancer occurred in some of the recruited patients). The median age of diagnosis was 49 years, almost 20 years younger than that of the general population. The findings from three other large-scale studies, using a similar questionnaire methodology, reported consistent findings of clinical features. Notably, Park et al (2006) and ten Kate et al (2007) selected their patient population to include individuals with MMR mutations only (Park et al 2006; Schulmann et al 2005; ten Kate et al 2007).

There has been no indication that a significant difference in the lifetime risk of SBC between MLH1 and MSH2 mutation carriers exists (ten Kate et al 2007; Rodriguez-Bigas et al 1998; Vasen et al 1996). Conversely data does suggest that males are at a higher risk than females, with a male to female ratio as high as 3:1 (Rodriguez-Bigas et al 1998; Schulmann et al 2005). Most adenocarcinomas demonstrate a compatible MMR phenotype, showing high-MSI at the molecular level (Koornstra et al 2009; Schulmann et al 2005). Similar to CRC in LS patients, SBC has been shown to occur at a younger age of onset, exhibit metachronous carcinomas and appears to have a better prognosis than patients with SBC in the general population (Rodriguez-Bigas et al 1998).

As visualisation of the small bowel remains difficult, surveillance guidelines do not appear within the scope of management for LS families. New visual techniques such as video capsule endoscopy (VCE) and double balloon endoscopy (DBE) improve the accessibility of the small bowel, however neither of these techniques provide the ideal solution. DBE remains too burdensome, time consuming and invasive for periodic screening while VCE, although less invasive, is limited by the inability to obtain tissue for histopathology.

In a recent paper by the German HNPCC consortium, the group proposed screening for SBC by gastroduodenoscopy as they demonstrated that SBC developed predominantly in the duodenum of their participants (Schulmann et al 2005). Ten Kate et al (2007) identified nearly half of their cases of SBC in the duodenum, also reporting a decreasing gradient from duodenum to the ileum in their Dutch population. The additional benefit of the gastroduodenoscopy is that it facilitates duel screening for gastric cancer and SBC. Schulmann et al (2008) argue strongly for this method to be used as a screening tool until the cost-effectiveness of different methods such as VCE has been determined prospectively.

2.8.7 PANCREATIC AND BILIARY CANCER

The significance of pancreatic carcinoma in LS remained enigmatic until Lynch et al (1985b) reported an association within the LS phenotype. In a larger study by Mecklin et al (1992), 18 patients with biliopancreatic cancer from suspected LS families were studied. Histological information was available on 14 patients. In 11, a biliary tract carcinoma was reported, in three a pancreatic carcinoma. A biliary tract carcinoma was suspected in the four patients without histological analysis. The study concluded that patients with suspected LS were at a greater risk of developing biliary tract carcinomas than pancreatic carcinomas. A recent report by Geary et al (2008) ascertained the pancreatic cancer risk in 723 individuals with a proven MMR mutation. Twenty-two cases of pancreatic cancer were identified, the majority in MLH1 and MSH2 gene mutation carriers (12 in MLH1, nine in MSH2 and one in MSH6). They identified a seven-fold increased risk for pancreatic cancer in individuals with LS as compared to the general population. Seventy percent of cases were under the age of 60 years and evidence of family clustering was noted. This has also previously been described by Lynch et al (1991), but biliary tract carcinoma within their cohort was rare.

The incidence of biliary tract carcinoma and pancreatic carcinoma within the LS spectrum remains low at 2% and 0.4% respectively (Aarnio et al 1999; Barrow et al 2009). No surveillance approaches have been successful in detecting pancreatic cancer at an early stage (Lynch et al 2008). The general census on screening is thus currently to discourage it as methods remain inefficient for routine examinations (Aarnio et al 1999; Lynch et al 2008). In addition, surveillance for biliary tract carcinoma is not recommended (Koornstra et al 2009). Notwithstanding, this has been appealed by Barrow et al (2009) who suggest that annual transabdominal hepatobiliary ultrasound and liver function tests should be performed from the age of 30 years, in families with billiary tract cancers (Barrow et al 2009).

2.8.8 URINARY TRACT CANCER

The risk of urinary tract cancer (UTC) in individuals with LS, has been reported to have a lifetime risk of up to 12% (Dutch population), 10% (Finnish population), 8% (combination of Danish, Dutch, Finnish and USA) and 3.2% (North Western England) (Aarnio et al 1999; Barow et al 2009; Järvinen et al 2009; Vasen et al 2001b; Watson et al 2008). While the bladder is the most common UTC in the general population, the renal pelvis and ureter are affected more frequently in LS (Crockett et al 2011; Lynch et al 2008). A large study conducted by Watson et al (2008) pooled data from four cancer registries to assess incidence estimates of Lynch-related cancers. A total of 6041 high-risk individuals of families with known MLH1 or MSH2 mutations were included in the study. The UTC risk in Watson's cohort was comparable to the Dutch and Finnish populations (Aarnio et al 1999; Vasen et al 2001b), while it was found to be markedly higher than that of the English families (Barrow et al 2008). It could be suggested that this difference in incidence may relate to the paucity of MSH2 mutation carriers in the English study as Watson and colleagues described MSH2 mutation carriers to have a greater risk when compared to MLH1. The highest risk for UTC is found between the ages of 50 to 70 years with males having a slightly higher risk than females for developing a UTC (Watson et al 2008; Van der Post et al 2010).

There is a suggestion that surveillance for early detection and prevention of UTC should be considered, especially among carriers of MSH2 mutations. Screening can be performed with ultrasound, cystoscopy, urine cytology and urinalysis (Barrow et al 2009; Koornstra et al 2009; Watson et al 2008). Vasen et al (2001b) recommend urinalysis with cytology and abdominal ultrasound, beginning at 30 to 35 years and on an annual to two-yearly basis. These authors limit screening to families with a history of UTC. Watson et al (2008) propose later surveillance, starting at 50 years, and suggest screening should be directed at MSH2 mutation carriers, and should not be limited to individuals with a family history of UTC. Koornstra et al (2009) recommend annual screening for haematuria by urine dipstick with cytoscopy and ultrasound if positive for haematuria. They advocate surveillance at 45-50

years and if a family history of UTC exists, surveillance is recommended five years prior to the earliest age of diagnosis within the family.

2.8.9 BRAIN CANCER

Brain tumours have been included in the spectrum of LS-related cancers (Aarnio et al 1999; Bermejo et al 2005; Lin et al 1998; Parc et al 2003; Vasen et al 2001b). Of all the cancers studied by Watson and colleagues (2008), brain tumours ranked the lowest, with a lifetime risk to the age of 70 years of 2%. As with the majority of extracolonic cancers, MSH2 carriers are at a higher risk than MLH1 carriers. This is clearly seen in the incidence figures reported by Barrow et al (2009), 0.6% risk of a brain tumour for MLH1 carriers and a 6.3% risk in MSH2 carriers. The median age of diagnosis of brain cancer is lower in individuals with LS than the general population with 26% of diagnoses occurring before the age of 25 years (Koornstra et al 2009; Watson et al 2008). The most common tumour type in LS is glioblastoma multiforme and astrocytoma (Koornstra et al 2009). Sarcomas are rarely described as part of the LS phenotype. However Geary et al (2008) report an eight-fold increased risk over the general population. Turcot syndrome, a variant of LS, describes the concurrence of colorectal adenomas and tumours of the central nervous system (Lallo et al 2005).

To date, no studies have recommended surveillance for brain tumours in LS. Given the absence of surveillance and low risk for developing this specific LS-related tumour, screening is not recommended (Koornstra et al 2009).

2.8.10 SKIN CANCER

Skin tumours have been described in LS. However, when characteristic skin lesions including sebaceous adenomas, epitheliomas and carcinomas occur with a visceral malignant disease, Muir-Torre syndrome (MTS) is suspected (Dores et al 2008; Ponti and Ponz de Leon 2005; Lalloo et al 2005). In 1981, Lynch and co-workers described MTS as a possible variant of LS, supporting

this argument by their description of MTS in a descendant of Warthin's family G (Lynch et al 1985a). Since then it has been postulated that the reverse of this may also be true as some cases of MTS may represent LS (Lynch et al 1981; Lynch et al 1985a; Ponti and Ponz de Leon 2005). Although MTS is predominantly associated with mutations in MSH2, mutations in MLH1 and MSH6 have been reported as a cause of MTS (Ponti and Ponz de Leon 2005; South et al 2008).

Surveillance for skin cancer in LS has not been recommended. Nevertheless, dermatological surveillance in MTS families is reasonable and early medical attention should be sought for skin abnormalities (Koornstra et al 2009). Ponti and Ponz de Leon (2005) support yearly dermatological examinations with wide local excision for the treatment of any skin carcinoma.

Table 4A and 4B compare data on published lifetime-related risks for CRC and extracolonic LS malignancies.

Table 6A: Lynch syndrome tumour spectrum: published studies of the lifetime cancer-related risk per mismatch repair gene mutation carriers.

Country	Gene	CUM % CRC			CUM % Extracolonic			CUM % endometrial (female)	CUM % gastric	CUM % biliary tract	CUM % urinary tract	CUM % ovarian (female)	CUM % brain	CUM % small bowel	CUM % pancreas
			M	F		M	F								
Denmark/Finland/ Netherlands/USA (Watson et al 2008)	MLH1								6.1		2.4	6.3	1.7		
England (Barrow et al 2009)	MLH1				38.5	29.7	44.8	29.2	10.9	3	2.8	5.5	0.3	4.5	0
France (Parc et al 2003)	MLH1							43							
Netherlands (Ramsoekh et al 2009)	MLH1	71						25							
South Africa (Stupart et al 2009a)	MLH1	92†													
USA (Lin et al 1998)	MLH1				11	5	19	19							
Denmark/Finland/ Netherlands/USA (Watson et al 2008)	MSH2								5.2		19.8	11.6	2.5		
England (Barrow et al 2009)	MSH2				35.5	23.8	47.8	24.4	7.8	0.4	4.1	7.5	6.3	1.3	0.7
France (Parc et al 2003)	MSH2							60.5							
Israel (Mukherjee et al 2011)	MSH2		61.6	61.1				55.6							
Netherlands (Ramsoekh et al 2009)	MSH2	77						49							
USA (Lin et al 1998)	MSH2				48	34	69	36							
Australia (Jenkins et al 2006)	Combined		45	38		67	72								
Finland (Aarnio et al 1995)	Combined							43	19	18	10	9			
Finland (Aarnio et al 1999)	Combined	82	100	54				60	13	2	4	12	3.7		

†Calculated on individuals who declined to undergo surveillance.
CUM-Cumulative lifetime risk (%).
CRC-Colorectal cancer.
Combined-combination of MLH1/MSH2/MSH6/PMS2.

.

Table 6B: Lynch syndrome tumour spectrum: published studies of the lifetime cancer-related risk per mismatch repair gene mutation carriers.

Country	Gene (MLH1 and *h*MSH2)	CUM % CRC			CUM % Extracolonic			CUM % endometrial (female)	CUM % gastric	CUM % biliary tract	CUM % urinary tract	CUM % ovarian (female)	CUM % brain	CUM % small bowel	CUM % pancreas
			M	F		M	F								
Finland (Hampel et al 2005b)	Combined	68.7	52.2					54				13.5			
France (Parc et al 2003)	Combined		89	78.5											
France Bonadona et al 2011)	Combined	35						34	0.7	0.6	1.9	8		0.6	
Germany (Plashchke et al (2004)	Combined				37										
Holland (Vasen et al 1996)	Combined	80	92	83				51.5							
Netherlands (Van der Post et al 2010)	Combined		70.1	56.6				35.4			7.5				
Netherlands (Voskuil et al 1997)	Combined	40.5	46	36											
Netherlands (Quehenberger et al 2005)	Combined		26.7	22.4		16	13	31.5							
Scotland (Dunlop et al 1997)	Combined					74	30	42							
Australia (Talseth-Palmer et al 2010)	MSH6	61						65							
England (Barrow et al 2009)	MSH6				43.1	28.4	53.9	48.8	10.4						
Holland (Hendriks et al 2004)	MSH6				33			71							
Netherlands (Ramsoekh et al 2009)	MSH6	75						61							
Sweden (Cederquist et al 2005)	MSH6		68.8	59.1				70.2				32.8			
USA/Canada/Australia/New Zealand/Netherlands/Scotland (Baglietto et al 2010)	MSH6		22	10		24	40	26							

CUM-Cumulative lifetime risk (%)
CRC-Colorectal cancer.
Combined-combination of MLH1/MSH2/MSH6/PMS2.

2.9 LYNCH SYNDROME – THE SOUTH AFRICAN CASE

The first documentation in SA reporting on a hereditary cancer resembling LS was described in 1985 (Goldblatt et al 1990). The family, NPC 1, was identified by a general practitioner (GP) working in a remote community near the Namibian border. The observation of a family history associated with a familial susceptibility to early-onset CRC was later recognised by a clinical geneticist collaborating with the GP to be typical of LS (Goldblatt et al 1990). The diagnosis of LS was made in 16 men on the basis of clinical, surgical and pathological data obtained from hospital records and anecdotal information from family members. None of the affected family members had extracolonic malignancies and the family was classified as type one LS. The age of affected family members ranged from 19 years to 68 years, with the reason for the male predominance unknown. As many of the males of this family worked within a secure diamond-mining village, it is suspected that news of the family, particularly of their sisters' health, was largely undisclosed, accounting in part, for the dearth of reported female cancer. A review of this family a decade later described 17 affected males and the identification of two affected females with CRC (Ramesar et al 2000).

The NPC 1 family were from the tiny village of Kommagas and of Mixed Ancestry descent. Many of the individuals from this family still reside within remote communities along the West Coast of SA including: Kleinsee, Kommagas, Nababeep, O'Kiep, Steinkopf, Springbok, Hondeklipbaai, Liliefontein, Nourivier and Port Nolloth (Figure A). To date the pedigree consists of 545 known members spanning five generations. Males and females are affected with CRC and extracolonic cancers have been recorded, albeit this being classified as a LS I family.

2.9.1 MANAGEMENT OF LYNCH SYNDROME IN SOUTH AFRICA

Colonoscopic surveillance services are restricted to established centres in tertiary hospitals in SA. As many individuals of the NPC 1 family lived more than 500 kilometres from the nearest centre an annual outreach endoscopic

service was instituted in 1988 offering endoscopic surveillance to all blood relatives of affected individuals from the family. Initially screening was only offered in one centre, a small mining town hospital in Kleinsee to which the family travelled. Later, with the growing burden of disease, the service expanded to include four centres along the West Coast of SA. Following the yearly screening programme, family members were recruited and offered the opportunity of becoming involved in research to determine the genetic cause of their familial cancer. Initially the mobile outreach service was limited to screening only, but later developed to create a platform for recruitment into research which led to the identification of the causative mutation in 1995 (Ramesar et al 2000). As the genetic basis of LS was known for NPC 1, a C1528T alteration resulting in a premature stop codon, producing an ineffective peptide within the MLH1 gene (Ramesar et al 2000), molecular genetic testing became possible for at–risk relatives. A predictive testing (PT) programme, based on the British protocol, was established in 1997/1998 (Appendix 1). NPC 1 was the first family to enter the PT and colonoscopic surveillance outreach programme. To date, 230 individuals have been found to carry the C1528T mutation.

The outreach endoscopic service is conducted annually to enable surveillance according to recommended screening guidelines. Consistent with the current SA policy, PT is only offered once the at-risk individual reaches the age of 18 years, with colonoscopic surveillance done earlier if symptoms are present.

2.10 PREDICTIVE TESTING FOR LYNCH SYNDROME

In LS, genetic testing starts with an affected individual. If a mutation is identified in a MMR gene, PT is offered to the individual‘s family members, as they are at-risk of carrying the mutation. A negative test result for a known mutation indicates that the individual is not at an increased cancer risk. However, if genetic testing does not identify a mutation in an affected individual, the results are uninformative and all members of such families are

advised to adhere to high-risk surveillance recommendations. For these families, genetic testing does not help determine which relatives may or may not be at an increased risk for developing LS-related cancers (Prucka et al 2008; de Wert 1998).

PT aims to provide future health-related information to the unaffected individual at a suspected high-risk of developing LS (Brain et al 2005; Evans et al 2001). Ideally this information can lead to the timely identification and knowledge of their mutation status enabling targeted screening to detect CRC at an early and potentially curable stage (Evans et al 2001; Järvinen et al 2000). The idea of PT and its possible implications, namely, to identify individuals who are predisposed to a disease that has not yet developed, is a difficult concept. Furthermore the uncertainty about whether or not the condition will develop, when it will appear and how severely it will manifest itself adds to the complexity of PT (Aktan-Collan et al 2001; Chapman and Burn 1999). There is thus a strong consensus that PT should be conducted within a framework of genetic counselling as the process of considering, arranging and interpreting such a test is not uncomplicated (Ensenauer et al 2005).

2.10.1 PREDICTIVE TESTING AND COUNSELLING PROTOCOL

PT protocols were originally developed in the context of Huntington disease, an incurable, usually late-onset, autosomal dominant neurodegenerative disorder (Evers-Kiebooms et al 2000; Harper 1996). The PT protocol was developed, not only to protect the test applicant, but also to assist healthcare professionals in dealing with the difficulties that may arise from the application of the genetic test, and, even more specifically, the test result. This extended protocol was implemented to facilitate reflection around the consequences of genetic testing in light of a condition for which there is no cure or preventative management. Numerous authors have highlighted that such extensive discussion and reflection may not be required by individuals contemplating PT for LS, as it is known to have reduced penetrance and that preventative

management is available (Aktan-Collan et al 2001; Bleiker et al 2003; Collins et al 2007; Esplen et al 2001; Lerman et al 1996; Meiser et al 2004). These studies give cognisance to the opinion that most individuals at a high risk for a cancer syndrome have been satisfied with a single pre-test genetic counselling session and that no long-term psychological distress has been reported by shortening the protocol. Moreover, when the psychological and decision-making outcomes were compared between 26 individuals attending either a shortened (single pre-test counselling session and test results delivered at second session two weeks later) or extended counselling protocol (two sessions prior to receiving test results six weeks later) for LS, no evidence of harm was identified (Brain et al 2005). The authors however, did suggest that in light of a shortened protocol, participants would benefit from having information on what to expect, suggesting that a preparatory leaflet or telephone call outlining the session could be provided. The shortened protocol of only one pre-test session is offered in SA.

2.10.2 PRE-TEST COUNSELLING

The pre-test counselling session provides the client with extensive information on LS and the process of PT. The inheritance and clinical features of the condition are discussed together with information on cancer surveillance. A well-recognised barrier to the transmission of information is the emotional state of the individual (Peters and Biesecker et al 1997) and, therefore, the psychological meaning of the disease and the potential impact of the test result are extensively explored. The aim of the pre-test session is to aid individuals in developing a sense of how they will cope with a favourable or unfavourable result (de Wert 1998; Ensenauer et al 2005; Peters and Biesecker 1997). It has been suggested that clients have an expectation of their test result attributing to preconceived notions, which in turn may influence their reactions when the test result is delivered (Evers-Kiebooms et al 2000; Prucka et al 2008; Trepanier et al 2004). Counselling is thus used to explore all the pros and cons of testing, motivations for testing and elucidates the counsellee‘s expectations, identifying and explaining any unrealistic views that they may have (de Wert 1998).

2.10.3 RISK PERCEPTION

Many clients enter into PT with a sense of confusion around genetic risk. This is understandable if one thinks about the various categories of probabilities: the chance of inheriting the pathogenic mutation, the chance of developing CRC if a mutation is found, the chance of developing other specific cancers, the chance that cancer may develop at a specific age and the chance that other family members (such as children) may inherit the predisposing gene (Peters and Biesecker 1997). Despite being able to review and explain these specific risk figures in counselling, risk perception is often based on more abstract factors such as the emotional and psychological aspects shaped by the client‘s experiences of cancer (Evers-Kiebooms et al 2000). Appreciating the psychosocial side can aid the counsellor in relaying information in a more understandable and sensitive manner to the client (Geller et al 1997; Prucka et al 2008).

2.10.4 INFORMED CONSENT

Once a decision is made for an individual to embark on the PT process, there is a mandate for informed consent to take place prior to any blood being drawn to safeguard an autonomous decision-making process (Prucka et al 2008). Informed consent is largely defined by the notion that decisions are made in a collaborative manner, between the physician and the competent patient, whereby the patient provides authorisation for the procedure in a voluntary manner based on a substantial understanding of the information (Appelbaum et al 1987). The components of informed consent have been comprehensively reviewed by the American Society of Clinical Oncology (1996) and Geller et al (1997) and it is imperative that certain issues are discussed before and after genetic testing is offered. The aspects relating to the PT protocol and consent include:

- **A discussion of the genetic test**. This includes information on the type of information that the test may be able to elicit, what it might not be able to show and the subsequent health risks and medical

management (American Society of Clinical Oncology 1996; Trepanier et al 2004).

- **Implications of the test result**. A PT provides a positive or negative test result, indicating an increased or lowered cancer risk for the individual undergoing testing. The health-related risks associated with a positive test as well as the risks, even after a negative test result, must be elucidated (Trepanier et al 2004). It is imperative that the individual understands that the identification of a pathogenic mutation does not equate to having cancer nor is it a certainty that cancer will imminently develop (Geller et al 1997).
- **Options for risk management without testing**. Should an individual not want to know his or her genetic status, intensive colonic surveillance, as recommended to a mutation-positive individual, should be encouraged.
- **Risk of passing on a mutation**. Individuals who are identified as mutation-positive have a 50% risk of passing on the mutation to each of their offspring, while those individuals, without the mutation, do not pass on the risk. The offspring (of the individual declining testing) should also be made aware of their likelihood of a risk and their parent, informed that, should their child be tested and a mutation identified, by way of implication, their result (the parent) will be known. Testing of minors (individuals under the age of 18 years) is largely dissuaded as a result of the potential emotional and psychological harm that may result (American Society of Clinical Oncology 1996; Borry et al 2006). The appropriate age for PT is assessed on the age of expression of the disease. If medical benefits of testing are not apparent in childhood, testing is postponed until such an age when the child reaches adulthood and is able to make an informed decision for her/himself. In the context of LS, PT is usually only offered to individuals over the age of 18 years (Aronson 2009; American Society of Clinical Oncology 1996; Prucka et al 2008).

- **Technical aspects of the genetic test**. This includes information on the detection rate, sensitivity and specificity of molecular genetic testing.
- **Costs involved**. Currently patients seen in the Western and Northern Cape are not required to pay for genetic testing due to the research nature of the protocol. Apprehension around the implication that genetic test results may have on health insurance are thus far less of a concern as reimbursement for testing is not requested from medical aids/insurance coverage companies.
- **Risks of genetic discrimination.** Should genetic testing limit coverage in obtaining life or health insurance, it is advised that the individual reviews policies prior to testing. Other legal and ethical complications may include the possibility of employment discrimination. The law governing the prohibition of discrimination of healthy individuals based on genetic test results is prohibited (Equal Employment Opportunity Commission 1995; National Information Resource on Ethics and Human Genetics 1983; Trepanier et al 2004) and may be beneficial to divulge during the discussion with the individual.
- **Risk of psychological distress.** Participants should be informed of the potential adverse psychological reactions that may result such as anxiety, depression or family dysfunctioning. Dorval et al (2000) identified that failure to anticipate the reaction to the result has the potential to lead to an increased emotional distress. Even if an individual is not found to carry the mutation, aspects of psychological and emotional disruption such as regret for making major life decisions, prior to knowledge of the test result or even survivor‘s guilt, could transpire. Notably, guilt could also be experienced if there is a possibility of passing the mutation on to an offspring (American Society of Clinical Oncology 1996; Geller et al 1997). Additional elements that need to be addressed are the timing and readiness for testing, family concerns and the preparation for the result session (Trepanier et al 2004).

- **Confidentiality.** The individual should be informed of the effort made to maintain their confidentiality and to keep the genetic information secure. It is also important that the individual is aware of other persons with access to the information. For instance, other medical professionals involved in their management or the referring physician (Geller et al 1997; Trepanier et al 2004). A potential ethical dilemma may evolve in maintaining the confidentiality of a client when seen at the same clinic that a family member is attending, especially when communication about the result has purposefully been restricted within the family (Prucka et al 2008).
- **Medical surveillance and screening (options and limitations**). Medical management following a positive test result can reduce the risk of developing CRC (Stupart et al 2009b; Järvinen et al 2000; de Jong et al 2004). Information on surveillance, optimal frequency of attendance and the limitations of the screening approaches should be provided. Recommendations for screening, even if the test result is negative, as per the general population requirements, must also be discussed.
- **Storage and reuse of genetic material.** This is of particular relevance in the research setting where a portion of the individual‘s blood sample may be kept for possible re-analysis for the benefit of other family members or for research purposes (subject to the Research Ethics Committees protocol).

The informed consent process attempts to empower the client, through the provision of extensive information, to facilitate a more thoroughly considered, educated and informed decision about genetic testing (Peters and Biesecker 1997). The PT protocol (including the informed consent document) is based on the general principles of medical ethics and includes:

- **Autonomy** - the principle of the right to choose whether or not to proceed with testing. This requires sufficient information to be given to the patient to allow for an informed independent decision;
- **Beneficence and nonmaleficence** - the principles of doing good and not harm requiring the informed consent to disclose all benefits, limitations as well as possible risks of the testing; and
- **Justice and confidentiality** - the assurance that the genetic information will not be disclosed to third parties such as other family members, insurance companies and employers (Beauchamp and Childress 2001; de Wert 1998; Ensenauer et al 2005; President's Commission 1983:6).

Implicit in the whole process is the right of the individual to decline testing at any stage without affecting their or their family member's future medical management (American Society of Clinical Oncology 1996; Ensenauer et al 2005).

2.10.5 POST-TEST COUNSELLING

Trepanier et al (2004) maintain that the result-disclosure session should take place during a face-to-face session with the client. Should the individual consent to being informed of their results, the disclosure and implications thereof are discussed at this stage, with special attention given to the possible emotional impact (Aronson 2009; Biesecker and Marteau 1999; Biesecker and Peters 2001; Raymond et al 2009). Peters and Biesecker (1997) state that the psychological reactions may need to be addressed in an ongoing manner, and follow-up sessions with the counsellor or a referral to a mental health professional may be required. The counselling of the post-test session is further dedicated to reviewing and co-ordinating the medical management and compliance with the screening protocol if needed (Peters and Biesecker 1997).

Aronson (2009) advises that the matter of disclosing the genetic result should be raised during the pre-test session to ensure that the client has already considered the issues of disclosure prior to testing. Another means to assisting the dissemination of information may be through the provision of written documentation (Schneider et al 2006).

Individuals who refrain from having biological children due to their concern over passing on a genetic risk can be enlightened to the possibilities of adoption, in vitro fertilisation with either sperm donation (if the father is mutation-positive) or ovum donation (if the mother is mutation-positive) and prenatal diagnosis (PND), including chorionic villi sampling, amniocentesis and cordocentesis. Should PND identify a mutation-positive fetus, selective termination of pregnancy is optional. Preimplantation genetic diagnosis (PGD), whereby the embryo‘s that are selected and implanted are screened to ensure that they do not carry the familial mutation is additionally available. However, some controversy about offering PND and PGD for late-onset cancer syndromes has been raised. Concerns relate mainly to the reduced penetrance of the condition, the onset of cancer in adulthood (excluding Familial adenomatous polyposis, which manifests in childhood), and the effectiveness of surveillance. In an extensive review of the literature by Offit et al (2006), no cases of PND could be identified for LS, whilst more than a dozen cases utilising PGD, have been reported.

Genetic counselling and PT should, where possible, be undertaken by those with experience to ensure that the issues of confidentiality and information provision are explained within the consent process (Aronson 2009).

2.11 PSYCHOLOGICAL IMPACT OF GENETIC TESTING ON THE INDIVIDUAL

For families with LS, knowing whether or not an individual carries the predisposing mutation can be of benefit as appropriate surveillance, which can reduce mortality and morbidity, can be carried out (Järvinen et al 2000).

Despite these benefits, the knowledge of being at a high lifetime risk for the development of associated LS cancers may result in psychological distress among mutation-positive individuals (Ashida et al 2009). Several articles, on the psychological impact of PT for LS, have shown that cancer worry, anxiety and depression have remained the same or only incrementally increased for mutation-positive individuals after the notification of the test results when compared to mutation-negative individuals (Bleiker et al 2003; Esplen et al 2001; Meiser et al 2004).

Further support for minimal psychological distress was offered by Aktan-Collan et al (2001) who evaluated the psychological consequences of undergoing PT for LS in participants selected from a research registry. During their prospective study, 271 healthy at-risk individuals from 36 Finnish LS families completed self-rating questionnaires. General anxiety, fear of cancer and death, and satisfaction with the future was determined at four intervals for both mutation-negative and mutation-positive individuals. Anxiety was measured using the 20-item State-Trait Anxiety Inventory (STAI), while fear of cancer and death and attitudes towards the future were assessed by five statements requiring a Likert-rated response. Measures were completed at baseline (before first counselling session), the result session, one month and one year after the test disclosure. The results of their study indicated that unaffected individuals who received a positive test result exhibited increased anxiety immediately after the disclosure of the test result. However, the differences between this group and the mutation-negative group disappeared during the follow-up period. Furthermore, testing seemed to relieve the fear of cancer in both groups and did not result in any harmful consequences at follow-up. In addition, all those tested viewed their future as promising and were as satisfied with their lives as they had been before embarking on testing. The decreased cancer fear, reported by the mutation-positive group, may relate to the notion that uncertainty is often more distressing than being identified as mutation-positive (Shiloh et al 2008).

Other studies have focused on the psychological impact of individuals within a clinical setting. Claes et al (2004), selected self-referred unaffected Dutch participants presenting for PT at a clinic-based genetic testing programme. Self-report questionnaires were used to gather information at pre-test (information and blood taking session) and post-test (one month after disclosure of test result) phases. General distress was measured by the STAI scale for which norm values for the Dutch population were available. Data was captured for 19 mutation-positive and 21 mutation-negative participants with mean scores on the STAI found to be within the same range or lower than the means in the general Dutch population. Differences between the two groups were not statistically significant for mean pre- and post-test scores. When considering the subgroup of mutation-negative individuals, however, differences between the two time periods were statistically significant ($p< 0.05$). Similar results for long-term psychological distress (three year follow-up) have been reported by an Australian study group (Collins et al 2007).

Key predictors of distress, in healthy individuals undergoing PT, include a history of depression (Murakami et al 2004), lower quality of life, social support (Arver et al 2004), complicated grief and the number of affected first-degree relatives (van Oostrom et al 2007). Findings from a longitudinal prospective survey highlighted that distress can be anticipated in cases where an extended family history of CRC or loss related to CRC are present (Esplen et al 2003).

The psychological impact of a positive genetic test result among cancer patients has been a relatively neglected topic in the literature (Vernon et al 1999; Esplen et al 2007). In individuals with CRC a positive test result indicates a risk of developing a second cancer and may therefore result in the individual being vulnerable to distress. During an American study involving 126 CRC patients three measures were used to determine psychological distress, STAI, CES-D (Centre for Epidemiologic Studies Scale) and RIES (Revised Impact of Events Scale). A subgroup of distressed individuals were

identified, whereby race and education were significantly associated with increased distress. Non-whites had higher mean scores than whites (STAI, $p<0.01$; CES-D, $p<0.01$ and RIES, $p<0.001$) and individuals with lower education levels had higher scores than those with higher education levels (STAI, $p< 0.01$; CES-D, $p<0.05$ and RIES, $p<0.01$) (Gritz et al 2005). In a larger study of 200 patients within the same population group, lower education and a poor support structure also determined higher mean scores on CES-D and STAI Scales. Additionally, younger age and non-white race were associated with increased levels of anxiety, whereas gender (being female) was associated with higher mean depression scores (Vernon et al 1997). Results of these studies suggest that the emotional reaction to a positive test result in a CRC patient should not be underestimated. Bonadona et al (2002), further propose that one cannot assume that the patient who has already had the diagnosis of cancer will consequently expect a positive test result. The authors identified more than a third of their patients having stated that the disadvantages of knowing their genetic test result outweighed the advantages. A favourable outcome, in this group of individuals, was identified by Esplen and colleagues (2007) who reported that distress levels were lower in individuals found to be mutation-positive, following a previous cancer diagnosis than those mutation-positive individuals (unaffected with cancer).

Published data from developing countries, on the psychosocial effect of being at-risk for LS, could not be identified for comparison purposes. It is not evident whether such countries would display similar or different trends to that of studies conducted in the USA, UK, Finland, Netherlands and Australia, as has been discussed in this review.

2.11.1 UPTAKE OF PREDICTIVE TESTING

The uptake rates of PT are variable. Survey‘s conducted prior to the availability of genetic testing for LS indicated that the majority (83%) of first-degree relatives of an individual affected with CRC, would request genetic testing if available (Croyle et al 1993). A large study undertaken in the USA,

selected both unaffected and affected family members eligible for genetic testing. Among these individuals, only 43% elected to have a genetic test. Noteworthy, of the 84 participants who provided a blood sample for genetic testing, eight declined to receive their test result when available to them (Lerman et al 1999). Interest in genetic testing was further explored in an Irish and an American study which identified a slightly increased uptake rate of 51% (Hadley et al 2003) and 64% (Peterson et al 2003), respectively.

The documented uptake rate reported by Hadley et al (2003) and Lerman et al (1999) was significantly lower than predicted by Croyle (1993). However figures from a study of the Finnish population (Aktan-Collan et al 2000) greatly exceeded those from the American (Peterson et al 2003) and Irish (Hadley et al 2003) study, suggesting that interest in genetic testing for a predisposition to CRC may be high. Aktan-Collan et al (2000) invited 446 at-risk unaffected individuals to participate in their study. The research was based on questionnaires, which were completed three times during the study period (before the initial counselling session, one month after and one year after test disclosure). Of the 446 eligible participants, 381 consented to the study and 88% (334/381) requested PT. The Finnish authors suggest the difference in uptake rates may relate to their health care system, where private health insurance does not play a major role and the majority of the population is managed by the public health-care system. Genetic testing and counselling in countries with a national health system remains expensive and has the potential to increase medical insurance policies which may collectively lead to decreased uptake rate.

2.11.2 BARRIERS AND FACILITATORS TO PREDICTIVE TESTING

Several sociodemographic and psychological reasons for not participating in PT have been highlighted in the literature. Among individuals undergoing genetic testing, higher education (Aktan-Collan et al 2000), being employed (Aktan-Collan et al 2000), higher pre-test risk perception (Codori et al 1999; Hadley et al 2003; Lerman et al 1996; Lerman et al 1999), and more frequent

thoughts about cancer (Codori et al 1999) are commonly identified in acceptors of PT as compared to decliners. Hadley et al (2003) also identified that individuals with a personal history of cancer or who are unaffected, but have a greater number of affected relatives with CRC, accepted testing more often. Individuals concerned about their ability to handle the emotional effect and the psychosocial effects on their family, pursued testing less frequently (Hadley et al 2003; Keller et al 2004; Lerman et al 1996), while the presence of depression has been identified to significantly reduce uptake rates (Lerman et al 1999). Studies conducted in the USA have highlighted that insurance coverage and concern over possible discrimination may also impede the pursuit of genetic testing (Hadley et al 2003; Kinney et al 2000).

Key motivational factors driving the pursuit of genetic testing for LS include: early detection of cancer, obtaining knowledge of the offspring's risk, the opportunity to reduce uncertainty as well as obtaining information that may reduce screening frequencies (Claes et al 2004; Esplen et al 2001; Esplen et al 2007; Hadley et al 2003).

2.11.3 BARRIERS AND FACILITATORS TO SURVEILLANCE

Screening for CRC facilitates the removal of polyps and the treatment of early tumours, preventing CRC mortality in LS. Despite the well recognised benefits of screening for CRC, adherence to these recommendations has been less than optimal (Järvinen 1995; Levin 1996; Lynch et al 1993b; Vernon et al 1997). Compliance with endoscopic screening guidelines has been studied extensively, with the rate of adherence ranging from 60% to 90% among first-degree relatives of CRC patients (Harris et al 1997; Houlston et al 1990; Kinney et al 2000; Mack et al 2009; Richardson et al 1995; Stephenson et al 1993) and from 58% to 99.5% in studies of LS families (Bleiker et al 2005; Hadley et al 2004; Halbert et al 2004; Järvinen et al 1995; Järvinen et al 2000; Liljegren et al 2004; Pylvänäinen; Stanley et al 2000; Stoffel et al 2003; Stupart et al 2009b; Wagner et al 2005).

Accurate assessment of compliance is complex as attendance for endoscopic screening, as used to determine compliance, have varied from study to study. Previous research groups have predicted compliance rates on the basis of the participant attending at one screening only (Stephenson et al 1993; Stupart et al 2009b), while other researchers have delineated specific screening intervals (annually, one to three years, and less frequently) (Hadley et al 2004; Stoffel et al 2003). Halbert and co-authors reported on yet a different categorisation of compliance: individuals indicating that they had received a colonoscopy within two years were viewed as compliant, while those never attending or seen three or more years ago were non-compliant. As colon screening can only be effective if high-risk individuals adhere to recommended guidelines, it is important to determine if screening every one to two years over a sustained period has occurred in the study participants. Secondly, the majority of studies focusing on LS families have obtained data from self-reported screening behaviours (Hadley et al 2004; Halbert et al 2004; Liljegren et al 2004; Stoffel et al 2003; Stoffel et al 2010 Wagner et al 2005), where attendance rate and time period between screenings may not be accurately recalled. The only study to utilise self-reported behaviour and combine this with actual uptake of screening (information derived from medical records), was conducted in the Netherlands. Bleiker et al (2005) determined compliance based on participant attendance rate to screening intervals every one to two years and identified these rates to vary between 84% (according to patient recall) and 72% (according to medical records).

Previous studies examining CRC screening practices have highlighted that certain sociodemographic factors can affect adherence to recommended CRC screening guidelines. Physician recommendation or advice (Rees et al 2008; Stephenson et al 1993) and family history of CRC (Gili et al 2006; McCarthy et al 1993; Myers et al 1990; Stoffel et al 2010) influence adherence rates positively, while a lack of formal education (Glanz et al 1999; Myers et al 1990; Sun et al 2004; Vernon et al 1997), lower income and socio-economic status (Vernon et al 1997; Weitzman et al 2001) and low literacy rates (Doak et al 1998;) are associated with poor patient compliance.

Other factors likely to reflect lower levels of adherence include age at participation (Denberg et al 2005) and gender (Codori et al 2001; Denberg et al 2005; Weitzman et al 2001). The literature, however, remains ambiguous on these two aspects, highlighting associations between a young (Denberg et al 2005; Gili et al 2006) and older age (Glanz et al 1999) as well as both male (Codori et al 2001; Gili et al 2006; Weitzman et al 2001) and female status (Denberg et al 2005). Additional barriers to screening include a lower level of perceived susceptibility to CRC (Glanz et al 1999; Lynch et al 1999; Denberg et al 2005; Vernon et al 1997; Wei et al 2004), fear of discrimination by insurance providers (Codori et al 2001; Denberg et al 2005; Guerra et al 2005; Lynch et al 1999), logistical obstacles (Denberg et al 2005; Price 1993), and population characteristics of a minority group including Japanese, Latino, Filipino and Korean (within the USA) ethnicity (Glanz et al 1999; Guerra et al 2005; Maxwell et al 2000). As these population groups are largely reflective of a lower socio-economic status, the socio-economic factors rather than the ethnicity may account for this.

A substantial body of research has highlighted that psychological factors impede on CRC screening. These include, a negative attitude toward screening procedures (Beeker et al 2000; Price 1993), fear of cancer (Kruger et al 2005; Natale-Pereira et al 2008; Subramanian et al 2004), a fatalistic approach (the belief that CRC is incurable) (Powe 1995; Price 1993), concern over the prospect that it may lead to colon surgery (Price 1993), denial (Lynch et al 1999; Price 1993), anxiety of finding cancer (McCaffery et al 2003), and a low perceived-risk of developing CRC (Natale-Pereira et al 2008; Lynch et al 1999).

2.12 IMPACT OF LYNCH SYNDROME ON THE FAMILY

2.12.1 COMMUNICATION OF THE GENETIC INFORMATION TO THE FAMILY

Once a genetic mutation has been identified in an individual, the result not only affects the proband, but extends to his or her biological family. Informing relatives about the identification of a pathogenic mutation allows unaffected family members the opportunity to ascertain their cancer-risk through mutation-specific testing and to determine if they require high-risk cancer screening (Stoffel et al 2008). Current standards of practice dictate that the responsibility of disclosing the genetic information to the at-risk family members lies with the individual (American Society of Human Genetics Social Issues Subcommittee on Family Disclosure 1998; Forrest et el 2007). Consequently, the dissemination of cancer-risk information and subsequent access to genetic counselling and testing services among relatives depends, partly, on whether or not the proband discusses the test result with family members. Family communication and timely disclosure of the health information is thus vital to ensure that at-risk family members are informed and understand the genetic information. Previous research has found that a high proportion of mutation–positive individuals do disclose their test result to their family. For example 81-85% of individuals, selected from a cancer registry, discussed their BRCA1/2 test result with a family member (Hughes et al 1999; Hughes et al 2002) and disclosure usually took place in a timely manner (95% of those who discussed their test result did this within a week) (Hughes et al 2002). Comparable figures have been published in clinic-based studies determining attitudes towards informing relatives about genetic testing for breast cancer (Julian-Reynier et al 1996; Julian-Reynier et al 2000). In the context of LS, an American study identified that 98% of individuals undergoing genetic testing informed their first-degree relatives of their test result (Stoffel et al 2008).

Overall, rates of communicating genetic test results tend to be lower when relatives are outside the immediate (nuclear) family (Bonadona et al 2002; Claes et al 2003; Forrest et al 2003; Kausmeyer et al 2006; Mesters et al 2005). One study identified a 23% decline in the rate of communication when second- or third-degree relatives were considered (Stoffel et al 2008). Indeed, information about genetic testing is most often disclosed to partners and/or siblings and less often to children and parents (Bonadona et al 2002; Peterson et al 2003).

Disclosure is less likely to occur when the patient perceives the information as potentially disturbing to the relative, if prior conflict or a lack of cohesion exists among family members or if there is an unwillingness to cause concern (Forrest et al 2003; Julian-Reynier et al 2000; Koehly et al 2003; Kohut et al 2007; Mesters et al 2005; Stoffel et al 2003). Additional barriers to communication, as far as breast cancer is concerned, include: adoption, divorce, remarriage, and a large age gap between siblings (Green et al 1997), while patients already affected with a cancer are more likely to disclose genetic information to their families (Julian-Reynier et al 2000).

Communication of a genetic test result can also be influenced by the mutation status of the individual (Patenaude et al 2006). Hughes et al (1999) identified that women receiving a mutation-positive BRCA result were more likely to convey the information to their family than those with a negative result. In a later study by the same author, a similar pattern of disclosure was described for sister pairs with a definitive result compared to those with an inconclusive result (Hughes et al 2002). Disclosure was additionally less likely to occur when an individual had younger children (Kohut et al 2007; Mesters et al 2005), as telling children about their genetic risk occurred around key life decisions, at a specific life stage or when they were old enough to understand (Forrest et al 2003). Motives for informing family members are largely to obtain emotional support, to encourage genetic testing and to promote the

provision of risk information to relatives (Green et al 1997; Hughes et al 2002; Mesters et al 2005; Stoffel et al 2008).

Women have been described to play a greater role in communicating at-risk information when compared to their male counterparts, and female relatives, rather than male relatives, are more likely to be informed about genetic testing, particularly in breast cancer (Hughes et al 1999; Koehly et al 2003; Wilson et al 2004). In the context of LS, where both males and females have a high risk of developing cancer, the impact of gender has not been as easily ascertained as that identified from the extensive literature available on breast cancer. However, in an Australian study investigating this phenomenon in LS patients, it was tentatively suggested that males may find the process of informing the at-risk relatives less natural than females (Gaff et al 2005). The authors further suggested that men, especially, may therefore benefit from professional support during the period of communicating genetic test results to the family. Patients have previously expressed difficulties with being the person responsible for transmitting the results to their family (Green et al 1997; van Oostrom et al 2007), however these individuals do not advocate for this role to be taken on by anyone else (Bonodona et al 2002; Forrest et al 2003; Kohut et al 2007).

Family communication remains a complex issue. Simply telling patients to inform their at-risk relatives about the implications of their genetic test result is insufficient. Even though the large majority of individuals are willing to share information about the presence of a gene mutation in the family and it has been reported that individuals do not deliberately withhold their test result from family members (Stoffel et al 2008), passive failure to disclose the result to the at-risk family does occur (Gaff et al 2005; Mesters et al 2005). This is of concern as the information can have life-saving implications.

It has been suggested that a detailed letter containing all relevant information around testing and especially which family members should be informed

about genetic testing may be of benefit in facilitating family communication (Peterson et al 2003; Stoffel et al 2008). Further support and strategies to augment communication may include genetic counselling, information pamphlets and regular contact by health professionals (Bonadona et al 2002; Green et al 1997; Gaff et al 2005; Peterson et al 2003).

2.12.2 ETHICAL ASPECTS: FAMILIAL NATURE OF LYNCH SYNDROME

When the family is not informed about the implications of the genetic information, the healthcare professional's duty to maintain confidentiality may be at conflict with their responsibility to inform the at-risk relatives about their susceptibility to the genetic condition (Lehmann et al 2000). An extensive review on the ethical guidelines and policies addressing the communication of genetic information in families was conducted by Forrest et al (2007). The general recommendations arising from this review are that the health professional, at the very least, informs the patient about the implications of the genetic information in light of its relevance for family members.

Certain guidelines permit disclosure when attempts to encourage the patient to disclose the genetic information have failed. Confidentiality may be breached and the genetic information released if the following criteria are met: —. (a) reasonable efforts to elicit voluntary consent to disclosure have failed; (b) there is a high probability both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; (c) the harm that identifiable individuals would suffer if the information is not disclosed would be serious; and (d) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed" (President's Commission 1983:6). In the USA, the healthcare professional is not required by law to warn the at-risk family members (American Society of Human Genetics 1998), while the European (European Commission 2004) guidelines take a stronger stance recommending that genetic healthcare professionals actively encourage disclosure. In contrast the German and French authorities strongly

advocate against disclosure if the patient does not inform the family of the genetic concerns, giving priority to the patient‘s privacy (Committee for Public Relations and Ethical Issues of the German Society of Human Genetics 2000; National Consultative Ethics Committee for Health and Life Sciences 2003). There is no SA law applicable to breaching confidentiality or towards warning an endangered third party (Taitz et al 1990).

Mostly, patients demonstrate an understanding of the implications of a positive genetic test result and consider it their duty to inform at-risk family members about the risks of cancer and screening options. However, refusal to warn at-risk family members is well recognised (Evans et al 2009; Dugan et al 2003; Falk et al 2003; Julian-Raynier et al 2000). In a survey of patients from a Canadian Colon Cancer Registry, only 73.5% of individuals were willing to give the health care professional permission to inform their at-risk relatives if they could or would not inform them (Kohut et al 2007). Suthers et al (2006), in an attempt to increase awareness among at-risk family members about the availability of genetic testing for a familial condition, sent out letters to at-risk relatives with the permission of the proband. The result was an uptake of genetic testing, among at-risk relatives, from 23% to 40%. Based on similar research conducted in Finland, 92% (n=236) of at-risk relatives approved of this form of direct contact (Aktan-Collan et al 2007). The direct approach may work well in countries where registries are available (Finland, Denmark and to an extent SA), whereby direct recruitment can be facilitated. The model may not be as effective in countries without comprehensive registries and mailed letters may not be effective where the population is of a low functional literacy level.

Importantly, it must be considered that at-risk relatives may not want to be informed about a genetic condition for which they are at-risk. On the contrary, they may consider the contact an invasion of their privacy, capable of causing financial and emotional harm (Baker et al 1998; Suthers et al 2006).

2.13 GENETIC COUNSELLING

Since the first introduction of the term ‗genetic counselling', by Sheldon Reed in 1974, many and varied definitions have been used to describe the profession (American Society of Human Genetics 1975; Fraser 1974; Kelly 1986; Kessler 1979; Shiloh and Saxe 1989; Street and Soldan 1998). One of the most widely published, is that from the American Society of Human Genetics (1975), which describes genetic counselling as a communication process around the occurrence or risk of occurrence of a genetic disorder in a family. In the three decades since the definition was proposed, genetic counselling has expanded beyond its traditional borders and importantly placed emphasis on the therapeutic relationship and need for emotional support (Bisecker and Peters 2001; Evans 2006; National Society of Genetic Counselors 2006; Resta 2006; UNESCA International Bioethics Committee 1995). The definition accepted by the National Society of Genetic Counselors (NSGC) enumerates three core aspects which are commonly integrated into the process of genetic counselling. These include interpretation and education and counselling which are expanded upon below:

- Assessing the chance of disease occurrence or recurrence based on the family and medical history;
- Facilitating patient education in terms of the genetics, testing options, management, prevention, ongoing research and available resources; and
- Counselling of clients to enable an informed decision concerning their choices and adaptation to the risk or condition (National Society of Genetic Counselors 2006).

Essentially, genetic counselling involves the interpretation of complex genetic data into information that is easily understood by the client and has the potential to help the client make and cope with the decisions relating to genetic diagnoses and results of PT (Bennett et al 2003; Pilnick and Dingwall 2001).

Genetic counsellors are healthcare providers with a specialised degree in human genetics and counselling. The profession is, however, practiced by a variety of professionals from many different disciplines including: clinical geneticists, genetic nurses, psychologists, social workers and other medical specialists such as neurologists, obstetricians and ophthalmologists. Traditionally, genetic counselling centred around prenatal and paediatric genetic services and decision-making around reproduction. More recently the field has grown to incorporate adult-onset genetic conditions, including the rapidly expanding field of cancer genetics. In the 2006 NSGC Professional status survey, 39% of genetic counsellors were practicing in the field of cancer genetics, the second largest contributor, followed only by the prenatal sector. Interestingly, the cancer field was the only sector to illustrate growth over the six-year period captured during the survey (34-39%) (Parrott and DelVecchio 2007).

A number of elements outline a genetic counselling session. The first, and perhaps most integral part, includes taking a medical and family history, usually recorded in the format of a three-generation pedigree (Aronson 2009; Baker et al 1998; Weil 2000). Verification of medical records such as pathology reports can provide clues when assessing hereditary cancer susceptibility as certain types of tumours are more likely to be associated with a genetic cause (Prucka et al 2008). For example, CRC tumours with MSI or other pathological features, as discussed under Section 2.6.3 and 2.6.4, may be suggestive of LS. The counselling session also includes educational aspects, whereby the client is provided with information on the genetic condition including the prognosis, management and treatment options. An assessment of reproductive or personal health including the hereditary aspects of the genetic condition are also discussed (Bernhardt et al 2000; Biesecker 2001; Harper 1998; Resta et al 2006).

If appropriate, informed decisions regarding genetic testing are made by the counsellee. A major tenet in the decision-making process is not to persuade

the counsellees to make certain decisions, but rather to assist them in making the best decision for themselves, taking into account their beliefs, values and circumstances (Baker et al 1998; Ensenauer et al 2005; Kessler 1997; Shiloh 1996). Traditionally, genetic counselling aimed to uphold this non-directive standard described as helping the clients reach a decision based on their personal perspectives without any particular guidance towards a decision (Evans 2006; Kessler 1997; Shiloh 1996). Elwyn et al (2000), however, argue that the counsellor should contribute his or her personal views to the counsellee if there is a medical benefit to a particular course of action. In the model, the counsellee‘s values are still respected, but cognisance is also taken of the opinion of the medical expert. The concept, ‗shared decision-making‘, can be applicable in situations such as those in LS where the individual clearly benefits from medical management.

The most powerful part of the genetic counselling session is the emotional support and psychological counselling which can help the counsellee prepare and cope with their genetic concerns (Baker et al 1998). Should genetic testing be available and appropriate, informed consent and the discussion of other ethical and or legal issues are addressed during the consultations.

2.14 SATISFACTION WITH GENETIC COUNSELLING SERVICES

Patient satisfaction is an important measure for assessing the quality of a health care service, as it reflects on the experience of care received from the patient‘s perspective (Charles et al 2006). Given the importance of patient satisfaction in genetic counselling and the role it plays in the continual advancement of the profession, several scales for assessing satisfaction have already been developed. These scales, available in quantitative and qualitative formats, evaluate different components of the patient‘s genetic counselling experience (Lea 1996; Shiloh et al 1990; Tercayak et al 2001; Veach et al 1999). Typically, three dimensions are usually assessed and include: (1) competence of the health care profession; (2) the health care professional‘s affective behaviour towards the patient or client and (3)

satisfaction with the administrative procedures including costs and convenience of the service (Shiloh et al 1990). Such evaluations facilitate the further exploration of counsellee needs from the service, identifying aspects where improvements can be implemented (Biesecker and Marteau 1999; Lea 1996).

Much of the research on patient satisfaction suggests that the majority of patients are pleased with the genetic counselling that they receive (Bleiker et al 1997; Bjorvatn et al 2007; Charles et al 2006; Collins et al 2000; Davey et al 2005; DeMarco et al 2004; Sagi et al 1998). In a study by Stadler and Mulvihill (1998) conducted in America, the level of satisfaction among 51 self-referred patients seen for breast cancer genetic counselling was reported to be ~~h~~high" amongst a significant proportion of women. Overall, the patients considered that the consultation was worth their time and money. Similarly, Nordin et al (2002) described Swedish patients referred for genetic counselling at an oncogenetic clinic (breast, ovarian and colorectal cancer referrals) as being ~~h~~highly satisfied". These and other findings have led to the belief that most patients view the genetic counselling session as helpful, valuable, informative and capable of addressing concerns adequately. What is more, counsellee expectations of genetic counselling are often exceeded, as highlighted by Charles et al (2006).

One possible explanation for the high levels of satisfaction may be the lack of awareness of what genetic counselling entails among counsellees (Davey et al 2005; Hallowell et al 1997). Bernhardt et al (2000) point out that educating counsellees about the process of genetic counselling, prior to the session, may be one way of promoting realistic expectations. Furthermore, Michie et al (1997) and Shiloh et al (1990), found that satisfaction is determined by the fulfilment of patient expectations, whereby patient satisfaction increases when expectations are in line with what is received from the counselling session. Perhaps most importantly, counsellors should be aware that their agendas may be very different from those of their clients.

Dissatisfaction with genetic counselling does, however, occur. For example, individuals receiving information on genetic testing that may be negative or inconclusive in nature, may assess genetic counselling as less satisfying (Shiloh et al 1990), while higher education, younger age, cancer-specific distress (prior to the genetic counselling session), pessimism and poor family functioning is negatively associated with satisfaction (Collins et al 2000; Tercyak et al 2004). Asking too many medical questions and not receiving enough medical information during the counselling session is also associated with counsellees who are less satisfied (Pieterse et al 2007). Bleiker et al (1997) conducted a pilot study on individuals with a family history of cancer attending a familial cancer clinic in the Netherlands. The authors identified several areas where dissatisfaction was expressed by the 36 counsellees. Receiving particular attention was the perceived lack of communication between the counsellor and other health care professionals, the limited involvement of the family doctor, inadequate information on the possible consequences of daily life functioning and a greater need for psychosocial support during and after the genetic counselling session. A survey, administered to patients who had received genetic counselling in the state of Pennsylvania (USA), highlighted additional areas amenable to improvement. Suggestions included more frequent outreach visits, more convenient parking, amalgamation of the cancer risk assessment appointment with other medical appointments and information of updates on ongoing trials. With regard to breast cancer patients, Bober et al (2007), identified that women who receive more complex information are likely to report lower levels of satisfaction.

Greater satisfaction may be achieved if the information, given to the patient, is adapted to their coping style. Nordin et al (2002) identified that _monitors' (individuals who seek more information on a particular health threat) are not only less distressed, but are more satisfied with information provision. _Blunters' (individuals who avoid information on a particular health threat) on the other hand, show the opposite, namely, that less information reduces psychological distress and increases satisfaction.

2.15 OVERVIEW OF SOUTH AFRICA: POPULATION AND HISTORY

SA lies on the southern most tip of the African continent. It is classified as a middle-income country, comprising nine provinces and recognises 11 official languages. The republic of SA has an estimated population of over 48 million people (Tait et al 1996; World Health Organization 2006), broadly grouped into Black (79.6%), White (9.1%), Coloured or Mixed Ancestry (8.9%), and Indian/Asian (2.5%) (Statistics South Africa 2005).

As a result of SA's troubled and turbulent political past, including the implementation of the 'apartheid' system in 1948, a three-tiered racial hierarchy was introduced in the country. The Population Registration Act of 1950 classified and registered all South African's according to race, which stratified the White minority population at the top of the apex, the numerically preponderant Blacks at the bottom and Coloureds (including other minority groups that did not fit into either White or Black population groups) in the middle (Adhikari 2005; Bank et al 2003; Coovadia et al 2009, Goldin1987; Williams et al 2008a). The system could often lead to individuals, from the same family, being classified into different population groups as a result of their physical appearance. An example of one of the classification criteria was the 'pencil test'. This involved sliding a pencil into the hair, if the pencil remained in place, the hair was deemed too curly to be that of a White person and the individual would not be classified as 'White', even if the rest of their family was labelled as that under the Act (Erasmus 2001; Watson 2007). The White population regarded themselves as the only civilised race and governed over the other population groups from 1948 to 1994.

During this time of White supremacy and racial discrimination, the existing property rights of any non-white person were nullified. The government passed the Group Areas Act (1950), segregating trading and residential zones by race (Beck 2000). This forced relocation, to racially defined areas, led to deliberate inferior living conditions. Reserved employment opportunities, separate and unequal education and public facilities (Separate

Amenities Act 1953) were destined upon any person without a light skin (Aflolayan 2004; Beck 2000; Johnstone 1976). These two Acts specifically, were so severely enforced that separate amenities such as churches, hospitals, libraries and public toilets, were established (Erasmus 2001; Walker 2001; Worden 2007). Needless to say, those designated for the non-white races were inadequate. Non-whites were also unable to travel through White areas. Passbooks (race identity books), which had to be carried at all times, were issued to Black individuals. This document recorded data on race classification; residence and place of work to ensure that migration into urban areas was controlled when Blacks worked in White areas. If Black individuals were identified within a White area without a passbook, they were subject to imprisonment (Terreblanche 2002; Watson 2007).

The ‗apartheid' government also targeted the education system, enforcing separate facilities with different schooling requirements for each race. Only White schools required compulsory attendance while those schools educating the Coloured and Indian/Asian race, did not. Education for the Black race, above that of basic skills, was restricted. The Bantu Education Act of 1953 stipulated that Blacks were to be educated only in accordance with their opportunities in life, which was primarily to serve as a labour force in the industrial sector (Worden 2007). As the Black schools provided lower standards of education, few non-whites were accepted into universities as a result of academic requirements (Johnstone 1976; Terreblanche 2002). Up until the late 1980's, more than 80% of South African university students were White (Beck 2000).

The forced relocation of more than four million non-whites into demarcated zones beyond the White suburbs had a devastating effect on families and the previously established communities (Beck 2000; Watson 2007). The areas reserved for the non-white races, limited to the rural suburbs, were devoid of job opportunities and infrastructure. Workers were burdened with high transportation costs and long commutes if they were fortunate enough to

have a job in the lucrative urban region reserved for the White population. Consequently, poverty and crime increased. The oppressive living conditions in these areas led to a greater prevalence of heavy alcohol abuse, violence and gangsterism (Adhikari 2005; Erasmus 2001; Watson 2007).

Democracy was attained in 1994, transforming the racially segregated South African society into a single multi-ethnic society governed by the African National Congress. While the post-apartheid constitution promoted equality for all races, because of the enormous costs involved in achieving equitable services, education and opportunities, the country‘s demographic profile still reflects trends of the previous racial inequality system of the Nationalist Government regime (Burgard and Treiman 2006). Socio-economic inequality remains. Today, elementary jobs are still largely filled by the Black and Coloured sectors, while clerical, managerial and professional positions are mainly occupied by the White and Indian/Asian races (Statistics South Africa 2005). The economical divide is further evident when considering the unemployment rate of 28.1% in Black, 17.1% in Coloureds and 4.1% in White population groups (Statistics South Africa 2005) and the large discrepancy in the average annual household income for Black families, R37 711 (USA$ 5 500); Coloured families, R79 423 (USA$ 11 700); and White families, R280 870 (USA$ 41 500) (Statistics South Africa 2005).

To negate this effect, the new South African dispensation is currently placing greater pressure on governmental departments and public institutions to redress the racial disadvantages of the past. Steps introduced include the implementation of affirmative action, whereby people who are suitably qualified, but from a previously disadvantaged group (Blacks, women and people with disabilities), are given priority in employment (Rankhumise et al 2001; Terreblanche 2002). Black economic empowerment, is another measure driven by legislation and regulation, offering preferential procurement to Black citizens in the financial, construction and tourism sector *(*Department of Trade and Industry RSA 2006).

2.15.1 PROFILES OF THE NORTHERN AND WESTERN CAPE COMMUNITIES

Figure 4: The geographic location of the Western and Northern Cape in comparison to the other provinces in South Africa.

The population structure of the WC and NC province is very different to the national profile as the majority of individuals are Coloured (WC: 53.9%, NC: 51.6%) and the main language spoken is Afrikaans and not a native Black language (Statistics South Africa 2005).

The WC, located on the south-western tip of the African continent borders the NC province in the North (Figure 4). The NC constitutes three times the land area of the WC, but only accounts for 1.8% (versus 9.7% in the WC) of the nation‘s population (Beck 2000; Bradstock 2005; Burger 2009). Due to the NC‘s geographical location, with the cold Atlantic Ocean as its western boundary, the area experiences extreme weather conditions with an extensive temperature range between the summer and winter months (Burger 2009). The NC is one of the least developed provinces of the country with the economy largely dependant on game farming, agriculture and mining. Many of the towns have developed around mining industries, and include Alexander Bay, Port Nolloth and Kleinsee (alluvial diamonds extracted from the shoreline), Kimberley (diamond mining), O‘kiep, Springbok and Aggenys

(copper mining) (Figure A). However, many of these operations have been suspended due to the uneconomical value of further mining as a result of depleted resources. For example, the De Beer‘s Mine at Kleinsee, the largest alluvial mine in the world, only employs 6% of its original employees (Ferreira 2010).

The WC boasts a more favourable geographical location, a Mediterranean climate, greater employment opportunities (particularly in the retail and textile industry) and a strong network of higher education institutions (Burger 2009). It is not surprising that the unemployment rate of the WC (17%) is lower than that of the NC (25.7%) (Statistics South Africa 2005). On average, no formal education, lower income and rural dwellings are more common to individuals from the NC than the WC (Bradshaw et al 2004). Many of the NC households still have unsatisfactory access to basic services such as electricity, water and sanitation facilities as well as education and healthcare. According to the 2001 Census, almost a fifth of the NC population have no formal school education (as compared to 5.7% of the WC population) and, of great concern, 54% of the NC‘s population live below the national poverty line (United Nations Development Programme 2004). Poverty and unemployment are often associated with the rural picture and the discrepancy between the two provinces extends into the income sector, with the average monthly household income in the WC being R3 234 (USA$ 470) compared to that of the NC, R 971 (USA$ 140).

2.16 HEALTHCARE SYSTEM IN SOUTH AFRICA

The restrictive policies of the ‗apartheid‘ system have had a pronounced effect on the healthcare services of the country and the health of its people (Coovadia et al 2009; Mooney and McIntyre 2008). Marked differences in morbidity and mortality between the different population groups exist as a result of the major inequities that were enforced. During this time, the infant mortality rate in Blacks was 82 per 1000 live births as compared to 13 in Whites. Further illustrative of the disparity was the 12 year difference in life

expectancy at birth between the Black and White races (Benatar 1995; Walker 2001).

Despite the implementation of major changes to healthcare policy and services, including the provision of free healthcare to pregnant women and children under the age of 7 years, the distinct mortality profiles still persist beyond the ‗apartheid' period (Burgard and Treiman 2006). The existing differences are explained by the strong relationship between socio-economic status (poverty, inequality, inadequate housing and poor education) and health (Coovadia et al 2009; Lalloo et al 2004; Mooney and McIntyre 2008; Steyn and Bradshaw 2001; Walker 2001).

The coefficient of inequality indicates that SA is still one of the most unequal societies in the world (Statistics South Africa 2005). Currently the healthcare service has developed into two sectors, fragmented along socio-economic lines, whereby the upper and middle classes of all races (14% of the population), are managed in the fee-for-service private sector, while the large remaining majority are entirely dependent on the public sector (McIntyre et al 2007). A substantial difference in healthcare expenditure exists between the two sectors, with the ratio of private to public spending per person being R9 500 (USA$ 1 278) and R1 500 (USA$ 201) respectively (South African Health Review 2000). The disparity also extends into the human resource sector, where one specialist doctor serves 500 patients in private practice, but nearly 1 100 in the public sector (McIntyre et al 2007). Further inequalities, within the public sector, exist in the distribution of infrastructure, level of care, financial aid and resources between and within the different provinces (Benatar et al 1995; Bradshaw et al 2005; Coovadia et al 2009; McIntyre et al 2007). The statistics portraying the number of public hospitals per province indicate that the WC has 54 state hospitals compared to the 27 hospitals in the NC (Statistics South Africa 2005).

In addition, the measures implemented to create parity in the public sector's less well-served areas, through severe budget cuts to the better-served areas, has lead to a reduction in the effectiveness of the existing health care institutions (Benatar et al 1995).

In summary, one of the most significant challenges facing the South African healthcare system remains the inequitable distribution of resources between the public, private, urban, rural and interprovincial sectors (Coovadia et al 2009; McIntyre et al 2007). Proposed healthcare changes to address this disparity include the move towards a National Health Insurance system to promote access, equality and sustainability for the healthcare system. However the precise nature thereof is still the subject of much discussion and debate (Department of health n.d; Mooney and McIntyre 2008). In a more positive light, SA is one of only a very few developing countries to have been able to introduce national disability grants and a pension system. The child support grant provides a sum of R250 per month (USA$ 31) per child younger than eighteen years and an older person's grant (old age pension), R1010 per month to males and females older than 60 years of age (USA$150) (South African Government Services: Child grants and older person grants 2010).

CHAPTER THREE: METHODOLOGY

CHAPTER THREE

METHODOLOGY

3.1 INTRODUCTION

In this chapter, the methodological process of the research is described. The reasons for the selection of the Husserlian approach and a discussion of its appropriateness are provided. The sampling method and data collection is discussed, followed by a detailed explanation of the data analysis. The chapter concludes with a description of the measures taken to ensure the validity/trustworthiness and the ethical considerations of the research.

The study involved three major components:

3.1.1 ANALYSIS OF EXISTING DATA PRIOR TO INTERVIEWING THE PARTICIPANTS

Extensive data is captured on each individual seen at the GESC. The registry information includes: the age of the individual at PT, gender, physical address, type of mutation, cancer status at genetic testing (affected or unaffected with cancer) and the attendance of colonoscopic surveillance. The latter was used to determine the adherence rate among individuals with LS (known mutation-positive genetic test result) in the WC and NC. This was calculated by obtaining the date of result disclosure (according to the genetic test report) and subsequent screening attendance (captured on database). The recommended age-related colonoscopic frequency was taken into account (guidelines recommend screening every two years prior to the age of 30 years and annually thereafter) and compliance was determined for each individual. Five adherence groups, based on the number of missed colonoscopies, were defined (Table 5). Individuals were selected for interviewing from each of these groups.

3.1.2 INTERVIEWS

Semi-structured face-to-face interviews were conducted to gather data from participants involved in the GESC. Information pertaining to the PT programme and the endoscopic surveillance service was explored and analysed.

3.1.3 RECOMMENDATIONS TO IMPROVE AND INCREASE THE UPTAKE OF THE SERVICE

Findings, which could improve the service, were relayed to the genetic and clinical team immediately after data analysis. Factors which were identified as impacting negatively on the access to and subsequent non-attendance and underutilisation of the GESC were identified. Recommendations, many of which were suggested by the participants, to address these aspects were proposed and implemented where possible.

3.2 RESEARCH DESIGN

The research used a ‗multi-method' approach of both qualitative and quantitative methods with a phenomenological design.

Qualitative research enables the researcher to probe and explore questions/items referring to personal meaning, identify facilitators and barriers to change, and to identify reasons for the success or failure of the existing interventions (Starks and Trinidad 2007). Furthermore, qualitative research can provide insight into an individual's actions, beliefs, thoughts and perceptions that quantitative methods alone cannot do (Broadhead 1980; Chen and Rossi 1983; McMillan and Schumacher 2001).

Phenomenology is rooted in the late 18th-century European philosophy (Holloway and Wheeler 1996), and has increasingly been used as a type of qualitative enquiry in the social sciences. With its focus on the explanation of

human phenomena, from the perspective of the people involved, it is an appropriate design for research in humanistic disciplines such as genetic counselling. Phenomenological studies provide insight into human experience through the use of thick descriptions provided by the individuals involved (Brink 1996). This method of conducting research focuses on the understanding of the social phenomena from the participant‘s perspective, in an attempt to uncover meaning and generate understanding of the particular phenomena (Denscombe 2008; Watson et al 2008). In addition, phenomenology attempts to capture experience without imposing assumptions regarding the reality of the experience, and seeks to reveal multifaceted and profound processes beyond the surface appearance (Holloway and Wheeler 1996).

The two broad fields of phenomenology, namely interpretive and descriptive, arise from the influence of two philosophers, Edmund Husserl and Martin Heidegger. Koch (1995) recommends appraising both philosophical approaches when choosing a research methodology. Husserl‘s philosophy emphasises the description of a person‘s complex lived experience whereas Heidegger‘s view requires the researcher to go beyond the description of the individual‘s life world by thorough analysis and integrating of self-interpretation of the recorded text (Carpenter and Suto 2008; Cohen and Omery 1994; Morse 1994). As this study sought to describe the GESC from the users‘ perspective, a Husserlian phenomenological design was employed to guide the research. This is supported by McMillan and Schumacher (2001) who state that a descriptive approach is complementary to an initial study of a specific phenomenon.

The Husserlian phenomenological approach describes the meaning of the life experience from the perspective of the individual involved; and strictly cautions against the researcher engaging in a subjective perspective or offering a personal interpretation of the meaning. A true description of the meaning is achieved through the process of reduction. This entails

disconnecting the description from any preconceived notions of the researcher, thereby seeing the phenomenon in its true essence (Carpenter and Suto 2008; Cohen and Omery 1994; Knaack 1984). According to Koch (1995) reduction is used to ensure the validity of the interpretation by avoiding the inclusion of the researcher‘s self-interest. Morse (1994) highlights the most common technique of achieving reduction, namely, by identifying and articulating assumptions prior to data collection and analysis.

In the research conducted for this study, the researcher examined her personal attitudes, beliefs and prejudices prior to the engagement with the data collection in order to be as objective as possible. Assumptions made were written down and discussed with the supervisors to ensure that neutrality was maintained and that an analytic account of reality could be captured.

Figure 5 presents an outline of the research methodology detailed in the subsequent section of Chapter Three. The figure can be used to follow the process of the study when reading through the text (Sections 3.3-3.9).

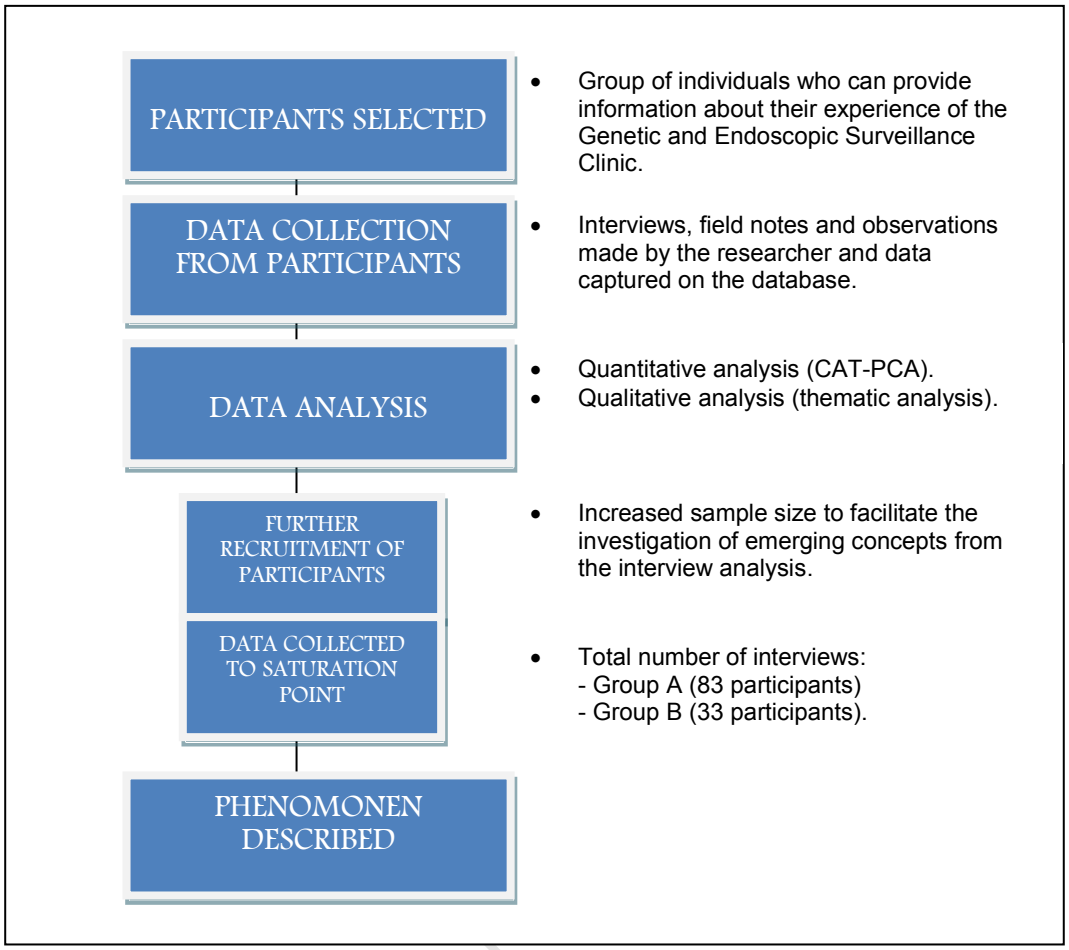

Figure 5: An outline of the methodology used during the study.

3.3 PARTICIPANTS AND SETTING

3.3.1 SAMPLING - METHOD AND SELECTION

More than 500 families have been recruited into the SA LS research programme. Disease-causing mutations have been identified in 37 of these families, 20 of which are currently involved in the PT programme (a pathogenic mutation has been identified in an affected family member and PT for any blood relative is available).

As a result of the founder effect in SA and limited geographical movement, the majority of these individuals live in the WC and NC Provinces. For many (especially those individuals from the rural areas) access to genetic testing

and surveillance is only through outreach services offered by GSH. For this reason uptake and result-giving of PT is limited to the time of the outreach service. Delivery of the result can occur only if the individuals present themselves at the outreach clinic. When the study was initiated, PT was available for 20 families. Eight hundred and thirty-five individuals had requested testing, and 631 of these individuals had received their genetic test results. Of the 216 individuals who tested mutation-positive, 191 were known to be alive.

Purposeful sampling was used to recruit individuals who could articulate their experiences of the phenomenon being investigated – the experience of being involved in a GESC. This form of sampling is commonly used in qualitative research as it facilitates the selection of participants who are able to give richness to the data (Brink 1996; Glaser and Strauss 1967). Clinicians, nurses or other staff members involved in the service, identified ‗information-rich' cases (from the list of individual's fulfilling the inclusion criteria, Section 3.4.1). Such cases were, therefore, appropriate for detailed study and of particular interest with respect to the research questions. In order to fully describe this experience, the researcher selected two study groups. This allowed her to concentrate on areas of particular salience to each group, which seen together, could provide a more detailed and accurate account of the topic being studied. For example, individuals entering into PT were interviewed to gain information on the PT phase, while those individuals who had already received a mutation-positive result and had been recommended to maintain regular colonoscopic screening could provide information on the surveillance aspect. Once the interviewing process was initiated, ‗snowball' or ‗chain sampling' was further implemented in the recruitment process of the individuals already involved in the service. This involved a process whereby the participants recommended relatives to be interviewed, and these relatives recommended other family members to be interviewed.

Individuals selected for interviewing and meeting the inclusion criteria were contacted by the Colorectal Cancer Genetic Co-ordinator (CRCGC) and the background and purpose of the study were explained to them (Appendix 2). The names and telephone numbers of those individuals who expressed an interest in participating in the study were provided to the researcher by the CRCGC. Individuals who declined the invitation to participate were asked, telephonically, for their reasons for refusal. It was explained that the information would be used to explore the reasons for the drop-out rate. They were provided with a list of possible reasons from which to select their responses. These responses were grouped into categories including: ‗not interested', ‗fear of disclosure', ‗no time available', ‗inconvenient' and ‗other'. They were not coerced or persuaded, in any way, to provide reasons.

The researcher contacted the consenting participants and advised them about the length of the interview process. It was also mentioned that a successive interview could be requested, should the first visit exceed an hour and a half, or if the participant became tired during the interview/questioning process. The researcher provided the participants with a choice of venues, and the most appropriate and private venue was selected by the participant.

All participants contacted by the CRCGC and then subsequently by the researcher agreed to participate in the study.

The two groups of participants included:

- **Group A:** individuals who had previously been involved in the PT programme, who were mutation-positive and, therefore, recommended to adhere to colonoscopic surveillance. These individuals were required to be involved in the programme for at least a year so that compliance with colonoscopic surveillance could be determined (individuals pending their first screening appointment were excluded as they would have been unable to answer questions relating to the experience of the endoscopic sevices).

To ensure that a broad range of participants who adhered to the recommended surveillance as well as those who did not adhere were selected for interviewing, criteria for adherence to recommended screening practices were identified. Adherence was determined for the 191 mutation-positive individuals and the cohort was subsequently categorised into five groups demonstrating compliance with recommended colonoscopic surveillance. The groupings were based on the number of colonoscopies they failed to attend (Table 5).

Table 5: Adherence grouping (1-5) used to define and select the sample frame of the study (Group A).

Group A	Attendance[†]	Number of individuals within group	Number of individuals interviewed	Percentage
1	None missed	48	19	39.6%
2	1 missed	40	27	67.5%
3	2 missed	32	13	40.6%
4	3 missed	21	6	28.6%
5	>3 missed	50	18	36%
Total		**191**	**83**	

[†]The date of the result disclosure (according to the genetic test report) and recommended age-related colonoscopic frequency was taken into account when calculating attendance. The South African screening recommendations include biannual colonoscopies for an individual younger than 30 years and annual colonoscopies after the age of 30 years.

Group B: individuals who were embarking on PT between June 2009 and December 2010. These individuals were interviewed three times, initially at their information session (prior to testing), immediately after their result session, and one month after receiving their test result. The interviewing time frame (for Group B) was based on an 18-month period. This was determined by the length of time that it took to reach data saturation for Group A.

According to Morse (1994) saturation is reached when no further explanation or description can be obtained, with redundancy or duplication of ideas arising as a result of the exhaustive exploration. The total number of individuals interviewed to attain saturation for Group A and the total number of interviews conducted for Group B is presented in Table 6.

Table 6: Number of interviews conducted for Group A and Group B.

Group A		Group B	
A1	19	**Interview 1**	**33**
A2	27	**Interview 2**	**23**
A3	13	**Interview 3**	**22**
A4	6	**Completed all 3**	**22**
Total (A):	**83**	**Total (B):**	**33**

3.3.2 RESEARCH SETTING

Interviews took place in the participants' homes or private venues of their choice. Marshall and Rossman (1999) suggest that, as the setting of an interview can affect the content of the information provided, interviews should always be at the interviewee's convenience and is usually preferable for this to take place in their homes. When an individual is requested to discuss sensitive issues, a private venue is more likely to result in a true portrayal of the situation (Holloway and Wheeler 1996). By interviewing the participants in their home environment, the researcher could observe the home circumstances, family interaction and behaviour. This also offered a solution to individuals who experienced transport difficulties. However, the researcher was also aware that certain individuals did not wish the interviews to take place in their homes, for fear of disclosure of their mutation-positive status. In these cases alternate private venues were arranged. All venues selected provided convenience and privacy.

3.4 ELIGIBILITY CRITERIA

3.4.1. INCLUSION CRITERIA

Inclusion criteria for Group A required the participants to:

- Be over the age of 18 years, have received their genetic test result and be mutation-positive;
- Have known their PT result for longer than one year (to enable the calculation of compliance with surveillance);

- Be accessible for a personal interview; and
- Have consented to be interviewed and tape-recorded by the researcher.

Inclusion criteria for Group B required the participants to:

- Be individuals from a family where a pathogenic mutation has previously been identified and the participant is requesting PT;
- Be accessible for a personal interview; and
- Have consented to be interviewed and tape-recorded by the researcher.

3.4.2. EXCLUSION CRITERIA

Criteria for which individuals for Group A were excluded:

- Participation in a small qualitative research study being conducted during the same time period.

Criteria for which individuals for Group B were excluded:

- Individuals who were seen prior to or after the determined data collection period, June 2009 to December 2010 (period defined by the length of time taken to reach saturation point for Group A‘s interviews).

3.5 MEASUREMENT INSTRUMENTS

3.5.1 INTERVIEWS

Interviews, often presented as the _gold standard‘ of qualitative research, offer the researcher the opportunity to discuss past events by focusing on descriptions of what people experienced and the reasons for the manner in which they experienced these events (Barbour 2008; Marshall and Rossman

1999; Patton 2002). For the purpose of this study, a semi-structured interview schedule was selected as the most appropriate measuring tool, because it provided the researcher with the ability to engage in a dialogue with the participants, enabling in-depth exploration of the events and their experiences from the ‗insider perspective' (Holloway 2005). This approach is used when a researcher is familiar with the components of the phenomenon, but is unable to anticipate all the possible responses to a particular question. In semi-structured interviewing, the interview schedule is used as a rough guide to direct the conversation and content to be covered, while being sufficiently open in structure to allow in-depth probing of significant responses of the participants (Patton 2002). Thus the interviews are interactive and sensitive to the interviewee's views, ideas and language, while keeping the format flexible (Pope and Mays 2000).

The interview schedule included both open- and closed-ended questions. Closed-ended questions were used to capture the sociodemographic data and data from the different measurement scales (Cancer Worry Scale; Duke Anxiety and Depression Scale; Facilitators and Barriers to Adherence Scale; Genetic Counselling Satisfaction Scale; Knowledge of Lynch Syndrome; Satisfaction with Genetic and Endoscopic Services). The scale responses were either nominal or ordinal and were numerically coded to permit the use of nonparametric statistics to identify patterns and relationships within the data (Morse 1992). While many of the closed-ended questions could have been completed by the participant, the researcher completed them personally during the interview to ensure consistency as certain individuals were functionally illiterate. This also provided the researcher with an opportunity to get to know the participants and paved the way for more in-depth responses to pertinent and sometimes sensitive questions asked in the open-ended items.

For each open-ended question, probes and reflection were included to aid further exploration and description of the phenomenon (Holloway 2005;

Minichiello et al 1990). Neutral probes were listed to clarify responses if they were incomplete or inaccurately understood. The use of open-ended questions allowed the researcher to explore the participant‘s thoughts and experiences while closed-ended questions were used to collect ‗yes/no‘ or pre-categorised scales of various items. The questions were generated from the literature, discussions with the supervisors, CRCGC and clinicians at the GESC. The interview schedule was designed in such a way that the basic questions were answered first followed by the more difficult or personal, possibly sensitive, items. This ensured that the researcher could establish a rapport with the participant prior to requesting information that they might have found difficult to answer.

A cross-sectional design was used to gather information from each participant at one point in time only (Group A), while a longitudinal approach, consisting of three interviews (pre-, post-PT result and one month after test result) was used for Group B.

In order to obtain content validity of the interview schedule, it was reviewed by the CRCGC and the research supervisors to ensure that the items were comprehensive, easily understandable and the sequencing was appropriate. The information sheet and consent form (Appendix 3) were available in both English and Afrikaans. As the researcher is fluent in both languages, the interview was conducted in the language of the participant‘s preference. The same interview schedule was used for all participants, but the order of the items varied according to the trend of the conversation. The time spent with each interview depended on the amount of prompting required to answer each item comprehensively and the amount of personal information the participants wished to reveal. Interviews for Group A ranged from one hour to four hours. Group B‘s first interview ranged from 20 minutes to one hour, two to five minutes for the second interview and 15 to 35 minutes for the third interview.

3.5.2 INTERVIEW SCHEDULE (APPENDIX 4a and 4b)

Questions in the interview schedule were grouped into several categories. Figure 6 outlines which sections were answered by Group A and Group B respectively.

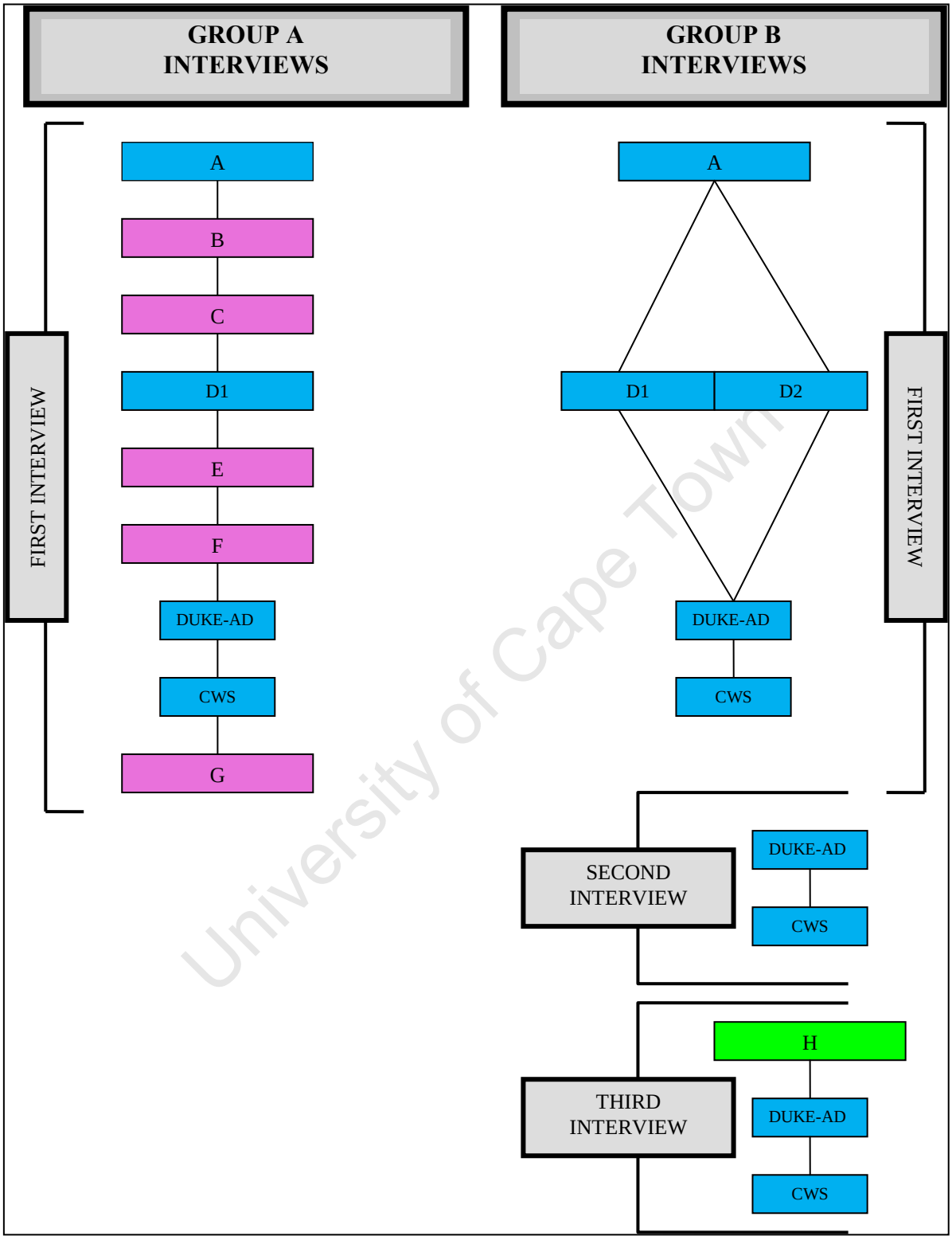

Figure 6: The interconnectivity of Group A and Group B interview schedules.
CWS-Cancer Worry Scale.
DUKE-AD-Duke Anxiety Depression Scale.

Section A – Sociodemographic Data and Personal History (Group A and Group B)

As it is best to start with questions the interviewee can answer easily, the first section utilised closed-ended questions to obtain information on the demographic background of the participant. A detailed family pedigree was drawn to provide insight into the family history of CRC, and formed an important process in establishing rapport with most of the participants. The participants provided information about the number of siblings, children, and individuals with cancer in the family.

Section B – Knowledge of Lynch syndrome (Group A only)

Knowledge of LS was assessed on a binary basis (knows/does not know) or by answering ‗yes' or ‗no' to questions. The scale used to assess the level of knowledge of LS was developed by Domanska et al (2009) and used to measure knowledge of LS amongst mutation-positive individuals in a Swedish cohort. The questionnaire contained 11 statements covering knowledge of CRC in general, LS cancer risk, surveillance, hereditary and genetic testing. As highlighted by Kasparian et al (2007), knowledge is not easily transferable between research studies as measures capture specific knowledge that may not be generalisable to other population groups or countries. This scale was thus revised to make it appropriate for the SA population, with the supervisors ensuring that the meaning was maintained after changes were implemented. This included changing item one, ‗CRC affects 5% of all individuals in Sweden' to ‗CRC affects 4-5% of all individuals in SA' and substituting the term ‗LS' where HNPCC had been used in the original scale. The Domanska scale was selected above the more well known Breast Cancer and Hereditary Knowledge Scale and the Breast Cancer Genetic Counselling Knowledge Questionnaire as the Domanska scale assesses the level of knowledge in LS families specifically, as opposed to assessing the background knowledge of individuals with a low to moderate breast cancer risk (Erblich et al 2005; Ondrusek et al 1999).

Open-ended questions obtaining insight into the personal interpretation of the participants' knowledge and their experiences of cancer were also included in this section.

Section C – Endoscopic Surveillance Service (Group A only)

The third section incorporated a combination of open- and closed-ended questions to obtain insight into the experience of colonoscopic surveillance. Reasons for adherence or non-adherence to the recommended colonoscopic surveillance was assessed by a three-point Likert scale ranging from "main reason' to "not a reason'. The responses provided to participants to select from, for attending or not attending surveillance, was based on the findings of Kruger (2005), whose study highlighted factors contributing to adherence and non-adherence to surveillance in the rural populations of the WC and NC. While many factors influencing surveillance have been cited in the literature (Esplen et al 2001; Hadley et al 2004; Liljegren et al 2004), Kruger's study was done within the population group selected for the current study and was, therefore, selected.

Section D1 - Satisfaction with the Genetic Counselling and Endoscopic Surveillance Service (Group A and Group B)

The participants' level of satisfaction with the genetic counselling service was assessed mainly, by means of quantitative measures. The ability to provide evidence for service development; to identify whether services are effective and of value to patients; and to ensure that the service is maintained or improved, is determined by the inclusion of these measures during the evaluation process (Payne et al 2008). The Satisfaction with Genetic Counselling Scale (SGCS) is a widely used assessment tool, designed by Shiloh et al (1990), used to measure patient satisfaction with genetic counselling (Davy et al 2005; Kasparian et al 2007; Payne et al 2008). The 32-item (later reduced to 12 items) questionnaire determines patient satisfaction with genetic counselling within three delineated domains, namely, instrumental, affective and procedural. "Instrumental' refers to the extent to

which the respondent evaluates the healthcare professional as having the required skills. ‗Affective' pertains to the client's perception of the healthcare provider in terms of the amount of time and interest devoted to them during their consultation. ‗Procedural' concerns the satisfaction with administrative procedures. Westwood et al (2006) used this instrument to develop their questionnaire, addressing satisfaction in primary care genetic services within the UK. In this present study, questions from De Marco et al (2004), Groenewegen et al (2005), Poulton (1996), Shiloh et al (1990) and Westwood et al (2006) were incorporated with other questions into the sections on consultation satisfaction.

As satisfaction with service is further linked to the process of service delivery during the PT programme, it was deemed particularly important to evaluate the genetic counselling session. The satisfaction with genetic counselling was assessed by using the recently developed six-item scale designed by DeMarco et al (2004), the Genetic Counselling Satisfaction Scale (GCSS). This scale was originally developed by Tercyak et al (2001), for use within the prenatal setting, and was validated by De Marco et al (2004) for use within the cancer counselling sector.

Section D2 - Predictive testing and counselling programme (Group B only)

Open-ended questions were used to determine the experience of being involved in a PT programme. Aspects of the clinic such as, referral pathways, purpose of genetic testing, and coping mechanisms were explored. Factors providing the motivation to undergo PT was determined by eight questions. Participants had to indicate the relevance of each statement as it related to their reason/s for engaging in the process of PT, by rating each statement on a three-point Likert scale ranging from ‗A lot' to ‗Not at all'. The list of items was based on a review of the literature and on the researcher's clinical experience in the field (Balmana et al 2004; Claes et al 2004; Esplen et al 2001; McAllister 2002).

Section E - Communication in the Family (Group A only)

Family communication can be determined by using the Family Communication Questionnaire (FCQ), consisting of a seven-item instrument developed to assess communication within four dimensions: (1) communication of genetic test result; (2) length of time between receipt of result and communication with relatives; (3) reasons for the communication of the test result and reasons for not informing the family of the result; (4) topics discussed with family members (Graham et al 1993; Rubin et al 1988). This study used an amalgamation of the FCQ and questions relating to family communication, sourced from the literature (Forrest et al 2003; Gaff et al 2005; Hughes et al 2002; Koehly et al 2003; McCann et al 2009; Peterson et al 2003; Stoffel et al 2008), which enabled further exploration of the communication process.

Questions relating to: factors used by the participants to aid the decision-making process of informing the family, the reaction of the family in response to the information, and the experience of telling the family, were also included.

Section F - General health of the participant (Group A only)

This section included questions which could determine the health-related status of the individual. The influence of testing positive for the gene predisposing to LS on alcohol use, smoking and a healthy lifestyle was assessed by the interview schedule, as was self-reported compliance/attendance with endoscopic screening. Surgery and/or chemotherapy/radiation histories were completed after the interviewing process by means of the clinical database.

Duke Anxiety and Depression Scale (Group A and Group B)

The Duke Anxiety and Depression Scale (DUKE-AD) screens both clinical anxiety and depression as diagnosed according to the psychiatric criteria of the Diagnostic and Statistical Manual of Mental disorders, Revised Third Edition (DSM-III-R) (American Psychiatric Association [*DSM-III-R*] 1994). The

scale investigates nervousness, depression, fatigue and insomnia, difficulty with concentration, being comfortable around people and giving up too easily. Each question is rated to reflect the intensity of the individual‘s emotions during the preceding week. The total score is calculated by adding each item‘s rating. A score of five or more (out of a possible 14) indicates major anxiety and depression (Parkerson et al 1990; Parkerson and Broadhead 1997). Validation of the DUKE-AD supports the scale‘s screener accuracy with operating characteristic curves of 78.3% for major depression and 72.3% for major types of anxiety (Parkerson and Broadhead 1997). Group A answered the seven-item scale once, while Group B completed the questionnaire on three different occasions (at the information and blood-taking session, immediately after the result session and one month after the result session), to determine the levels of anxiety and depression during the PT programme.

The DUKE-AD scale was selected as it was quick to administer taking just over two minutes to complete. As qualitative interviewing is a lengthy process, a measuring scale which is brief, but effective in providing information on the mental health of the patient, was preferred.

Cancer Worry Scale (Group A and Group B)

The Cancer Worry Scale (CWS) was originally developed to measure cancer-related distress, as a four-item measure, in patients with breast cancer (Lerman et al 1991a; Lerman et al 1991b). The scale determines how frequently patients think and worry about cancer as well as how often such thoughts or concerns affect their mood and ability to perform daily activities over a period of one month. The response options range from a score of one (not at all or rarely) to a score of four (all the time), with a minimum total score of four and a maximum total score of 16.

The CWS is commonly used to assess worry about cancer, and as with the DUKE-AD scale, it was selected for its brevity, taking a minute or less to

complete. The scale was administered once to Group A and three times (at the information and blood-taking session, immediately after the result session and one month after the result session) to Group B. The CWS has shown good validity (Gramling et al 2007; Lerman et al 1991a; Lerman et al 1991b).

Section G - Previous Research Involvement (Group A only)

As a large majority of individuals from SA LS families are at-risk as a result of the effect of a founder mutation, numerous national and international research studies have focused on this cohort (Anderson et al 2007; Blokhuis et al 2008; Burn et al 2008; Felix et al 2006; Goldberg et al 1997; Ramesar et al 2000). It was, therefore, important to determine the impact that inclusion in research studies was having. The willingness of the participants in this study, to partake in future research, was explored during the last section of the interview.

3.5.2 AUDIOTAPE RECORDINGS

Audiotape recordings are the primary means of capturing the data of qualitative interviews. Although this technique may appear, at first, to be intrusive, it allows the researcher the opportunity to foster a dialogue with the participant, rather than only asking questions and having to interrupt the conversation and engagement by having to write down the responses (Carpenter and Suto 2008). An additional advantage of recording the interview is the ability to create an accurate written record of the discussion which can be converted into text through the transcription process.

3.6 PROCEDURE

3.6.1 PILOT STUDY

A pilot study was conducted on two participants from each group, to refine the structure of the interview schedule and to identify any changes needed to improve the clarity and format. Questions were tested for difficulty of comprehension and to ensure that answers elicited the type of information

envisaged (Barbour 2008; Brink 1996; Roussow 2003). Piloting also allowed the opportunity to investigate the feasibility of the study, to ensure that the data obtained was observable and measurable (Barbour 2008; Brink 1996).

Following each pilot interview the researcher asked the interviewees for their critical opinion on any confusing categories or any other aspects of the schedule which could be considered insightful (Holloway and Wheeler 1996; Marshall and Rossman 1999; Roussow 2003). Several questions were adapted to eliminate their ambiguous nature and to aid the clarity of the interview schedule. Subsequent to these corrections, the schedule was rechecked by the researcher‘s supervisors. The participants in the pilot study were not included in the study. However, in addition to serving as a pre-test of the interview schedule, it provided an estimate of the amount of time required to complete each interview. Interviews for Group A took an average of just over an hour and a half, interviews exceeding this time span entailed a second home visit to complete. The interviews for Group B were, on average, 45 minutes (first interview), three minutes (second interview) and 20 minutes (third interview). Individuals from Group B were interviewed after their clinic appointment (in a private room away from the clinic) for the first two interviews, followed by a home visit (or any other private venue of their choice) for the final interview. Participants were informed about the three interviews, including the likely duration thereof, prior to consenting to the interview to ensure that they were able to commit this time to the research.

3.6.2 RECRUITMENT

Study participants for Group A were selected on the basis of having undergone experiences about which the researcher wanted to gain information. Potential participants meeting the inclusion criteria, accessible and likely to be willing to participate, were selected from the LS database by the CRCGC familiar with these individuals. As far as possible, individuals representative of a generalised broad base in terms of socio-economic status, education level and attendance category (Group 1-5) were selected and

contacted telephonically by the CRCGC, and invited to participate in the study. She then, with the permission of the individuals, provided the contact details to the researcher who then made contact with them to arrange the convenient interview times and venues.

Group B comprised any individual, entering into PT (during the period of June 2009 to December 2010) and meeting the inclusion criteria, who consented to the three-step interview process. These participants were also initially approached by the CRCGC, at their first PT session, to determine if they were willing to participate in the research study. They were then seen by the researcher following the first counselling session. Every individual invited to participate in the study consented to the interviewing.

3.6.3 IMPLEMENTATION OF INTERVIEWS

Each interview took place in a private venue of the participant‘s choice. The researcher conducted every interview personally during the months of June 2009 and April 2011 (including final (third) interview of Group B). In total 116 individuals were interviewed.

The aims of the research were explained to each participant, prior to interviewing, highlighting the benefit that their honest answers would have on improving the programme. Reassurance was given that all information discussed would be kept confidential apart from the possibility of being published in a scientific journal where names would not be used. It was re-iterated that other family members would not be discussed to maintain their confidentiality. The participants were reassured that their recommendations would be relayed to the genetic and clinical team so that they could be implemented in the service, but that their names would not be mentioned.

The participants (Group A and B) were advised that some of the questions in the interview schedule could revisit personal sensitive issues and that they

would be given the option of further counselling following the interview to address any distress caused by talking about their experiences and the contact details were provided.

Each audiotape was dated and labelled with a code. The participants' names were kept separately from the tapes and interview schedules and only the researcher had access to these. Tape recordings of the interviews were transcribed verbatim, in either English or Afrikaans, by the researcher immediately afterwards.

When quotes were incorporated to substantiate the participants' responses, the wording was changed so that it portrayed the meaning of the statement. This was particularly important to consider as the majority of interviews were conducted in Afrikaans, and lost their meaning when directly translated into English. Denscombe (2008) describes the process of transcription to include "tidying-up and editing" to ensure that the meaning of the data is conveyed to the reader. While the information may lose some of its authenticity when dealt with in this manner, Carpenter and Sumo (2008) claim that it is rather the meaning that matters, not necessarily the words. To ensure validity during this process, supervisor checks were incorporated to warrant that the interpretation did not change the participants' meanings.

3.7 TRUSTWORTHINESS AND VALIDITY

The validity of a study is closely linked to the researcher's ability to ensure that an appropriate meaning has been derived from the specific deductions made following data analysis. As Morse (1994) pointed out, the qualitative researcher is interested in discovering and learning about the truths as known to those participants being studied. Thus if the thoughts and ideas of the participant are accurately reflected by the researcher, trustworthiness of the data can be established (Holloway 1997). Using triangulation, the use of different methods of data collection, the validity of the study can be increased, as the strength of one approach compensates for the weakness of another

approach (Daly et al 1997; Golafshani 2003; Marshall and Rossman 1999; Patton 2002; Sarantakos 1993). A combination of different data sources including, observations, interviewing and analysis of database records was used to validate and cross–check findings during the data analysis.

Lincoln and Guba (1985) proposed that the fundamental criterion for qualitative research is trustworthiness and that the criteria for judging qualitative data include credibility, dependability, confirmability and transferability (Ulin et al 2005). Each of these aspects and their application in the researcher‘s study is briefly described below:

3.7.1 CREDIBILITY

Credibility focuses on the confidence in the truth of the findings of the study and the provision of an accurate understanding of the context (Carpenter and Suto 2008; Ulin et al 2005). This study utilised peer review in an attempt to ensure credibility. The researcher regularly met with her neutral co-supervisor during the analysis phase, to ensure minimal researcher bias in the interpretation and categorisation of the data and subsequent content analysis. Furthermore the interviews were electronically recorded and the data were captured verbatim during transcription by the researcher to enhance the validity by providing an accurate and complete record (McMillan and Schumacher 2001).

3.7.2 DEPENDABILITY

According to Holloway (1997), for a study to be dependable it should demonstrate consistent and accurate findings. A detailed description of the research method is thus given to ensure the decision trail is clear, process is consistent and results are dependable (Holloway 1997; Minichiello et al 1990). Field notes indicative of the date, time and location, were kept on all subject matter discussed between the researcher and her supervisors, the CRCGC and the participants. In addition, the CRCGC and co-supervisor, who

dealt with the qualitative aspects of the study, reviewed the interview schedule to ensure that the content was comprehensive and the questions were easily understood.

3.7.3 CONFIRMABILITY

The researcher made a conscious effort to maintain the distinction between her personal values and those of the participants to ensure that the findings were the result of the research and not due to subjectivity and her personal biases. As described by Morse (1994), confirmability pertains to obtaining direct and often, repeated affirmations of what the researcher has heard during the interview process, with respect to the phenomenon being studied. The researcher returned to the participants to confirm the findings and re-check interpretation of the emerging data to establish their confirmability.

3.7.4 TRANSFERABILITY

Transferability relates to the conclusions of the study and the possibility of accurately applying these to other cohorts or situations. The goal of transferability is to produce data which can be applied to other contexts if samples are selected to represent viewpoints and experiences that reflect key issues in the research problem (Minichiello et al 1990; Ulin et al 2005). Similarities to other parallel situations can contribute to extending knowledge on the phenomenon (Morse 1994). The use of comprehensive descriptions enables peers and/or readers to decide if the findings described may be extended and applied to different contexts or settings.

Qualitative research is concerned in deriving a true representation of reality as portrayed by the participant sample (Holloway 2005; Watson et al 2008). It derives its validity from the thoroughness of its data analysis and not from the representativeness of its sample as is customary in quantitative research (Cronin et al 2010; Watson et al 2008).

The use of the pilot study together with the supervisors' comments on the validity of the interview schedule ensured further trustworthiness (Holloway and Wheeler 1996; McMillan and Schumacher 2001).

In quantitative research, validity determines how truthful the research results are and whether the research instrument measured what it intended to measure (Golafshani 2003). Marshall et al (2000) suggest that the use of unpublished or nonvalidated measures can produce biased results and apart from selecting the quantitative measures for their brevity, they were additionally chosen as they had been tested for validity. The DUKE-AD measurement (Parkerson and Broadhead 1997; Wu et al 2002), the CWS (Gramling et al 2007; Lerman et al 1991a; Lerman et al 1991b), and the GCSS (De Marco et al 2001; Tercyak et al 2001) have all shown good validity in several international studies.

3.8 RELIABILITY

In qualitative research the most common technique of ensuring reliability, used by Husserlian researchers, is bracketing. This requires the researcher to bracket the emerging data from the rubrics of earlier descriptions, guarding against the influence of these on the phenomenon (Cohen and Omery 1994; Koch 1995). This was ensured by having the qualitative supervisor check that the meanings, derived from the interviews, were reflective of the discussions and that the themes derived were congruent.

In quantitative research reliability refers to the consistency of the measurement or the degree to which the measure can re-measure with the same subjects under similar conditions. A reliable measure will illustrate comparable test scores if conducted twice. Cronbach's alpha is commonly used as a measure of reliability (internal consistency) and involves only one administration of the test instrument unlike test/re-test estimates which require two administrations. A 'high' Cronbach's alpha value indicates that the item measures an underlying construct and a reliability coefficient of 0.7 or

higher is considered acceptable. In essence computing the alpha coefficient provides an indication of the measurement of fit, where a higher value represents a better fit. Eigenvalues (discussed further on page 112) are also capable of providing an indication of the fit (total variance explained by the measurement item) and are better suited when ordinal values rather than metric variables are being analysed.

3.9 DATA ANALYSIS

3.9.1 QUALITATIVE DATA

Transcripts of interviews provide the descriptive record but cannot provide explanations (Pope and Mays 2000), and therefore data analysis is required to facilitate the process of bringing order, structure and interpretation to the mass of collected information (Marshall and Rossman 1999). Such a systematic process is capable of reducing the amount of data to enable the researcher to make connections, identify categories and patterns of meaning (Carpenter and Suto 2008). This process usually starts early, during the data collection phase, and guides the ongoing data collection (Watson et al 2008). The advantage thereof, is that the researcher can refine questions and pursue emerging avenues of inquiry for further depth (Pope and Mays 2000).

The qualitative data analysis of this study was based on a thematic analysis approach (Colaizzi 1978), which incorporated descriptive principles as used in Husserlian phenomenonology. The analysis involved a process of data reduction, data display, drawing of conclusions and data verification. This is described in further detail by steps one to seven:

1. Reading of each participant‘s verbatim transcript with a focus on the aims of the study. This allows the researcher to acquire familiarity with each case and a sense of the full picture;
2. Statements, words or phrases seen as significant to the phenomenon are extracted from the transcripts (Coding and categorising data);

3. Meanings are derived for each significant statement;
4. The meanings are organised and data collected from each participant is constantly compared to that of other participants leading to theme development. Theme and sub-theme categories are established;
5. A rich and exhaustive description of the phenomenon is formulated;
6. The phenomenon is clarified;
7. Process of validation (Carpenter and Suto 2008; Colaizzi 1978; Sarantakos 1993).

Interviews were recorded to preserve the data on tape, allowing for the analysis to be completed subsequent to the interviewing. As the analysis was done following the communication process, the data could be analysed without influencing the communicator in any way (Roussow 2003). Once the recordings were transcribed verbatim, the coding of the data, which fragments the interviews into separate categories, allowed for the raw data to be processed (second step in Colazzi‘s approach). The initial categories for sorting the data were based on the literature and the researcher‘s background knowledge of the families at risk for LS. Codes were then assigned to each category, with the coded material used to explain the nature of the participant‘s experience. Although several topics had been predetermined based on the structure of the interview schedule, themes within these topics and their relatedness to one another emerged from the interview rather than hypotheses being created, a priori. The coding was then confirmed by the researcher‘s supervisors before further analysis took place.

The transcripts were read through several times, and the content was compared with the earlier collected data. The constant comparing and contrasting of categories identified patterns of meaning, recurring ideas and significant themes (Holloway 1997), with each category reflecting a concept being analysed to describe the participants‘ understanding and experience of the GESC. Any new information obtained from subsequent interviews, was converted into new categories for further analysis. The analysis was an

ongoing process, whereby the findings of the study drove the sampling process as the study progressed. Frequency tables were used to categorise the responses into descriptive statistics such as percentages and means. This could provide a summary of the categories of some of the aspects of the interview (Pope et al 2000).

Quotes were used to illustrate specific views held by participants, reflect the content or context of themes and sub-themes or to illustrate typical or unusual statements (Cronin et al 2010; Sarantakos 1993). Deviant cases were highlighted and the differences described. Once no new insights emerged, the point of saturation was declared for the specific category as new data would not contribute to further understanding. This was continued until all the categories reached saturation point (Daly et al 1997; Minichiello et al 1990). The data was then compared with the available literature.

3.9.2 QUANTITATIVE DATA

The Quantitative data, such as the demographic information, knowledge of LS, satisfaction with the surveillance and PT programme, DUKE-AD and CWS measures, were gathered during the interviewing process and captured on Excel spreadsheets.

The analysis involved a two step process. The first step analysed the mutual relationships between the items within the data set using Categorical Principal Component Analysis (CAT-PCA). CAT-PCA is part of the procedure option in SSPS, a software package for data management and statistical analysis (SPSS 2001). CAT-PCA is appropriate for data reduction and identification of underlying components of a set of items when variables are categorical (for example ordered categories). The primary benefit of using CAT-PCA rather than the traditional PCA, is that the restrictions of linear relationships do not apply. The scaling technique remains stable when sample sizes are small or large avoiding the difficulty in interpreting large numbers of parameter estimates required by log-linear models. CAT-PCA can perform non-linear

analysis on variables with different measurement levels such as nominal, ordinal, interval or ratio. The original set can be replaced by a smaller one with as little loss of information as possible. These items are then projected as vectors into a two or more dimensional space, whereby the length of the vector relates to its relative contribution to a particular dimension. Components which are grouped together by means of clusters of responses are known as dimensions[1]. The angle between the vectors represents the level of association between the vectors. Thus the technique illustrates a strong visual ability to identify potential relationships among variables and objectscores (participant's responses) in a multidimensional space.

Secondly, if applicable, the items were rescaled by transformations invariant to the level of measurement of the items (if the level was not violated) and all subsets transformed into one or more scales, dependant on the underlying dimensions of the construct. Eigenvalues[2] were calculated to indicate how successful the maximalisation and minimalisation criteria were. The component loadings[3] (co-ordinates of the vectors) and mutual relationships of these scales were subsequently analysed by appropriate multivariate techniques.

3.10 ASSUMPTIONS

The researcher assumed that each participant answered questions and provided unsolicited information honestly and expressed a true reflection of their experience.

[1] Dimensions are labelled by the common characteristic of the variables that determine the particular dimension. They are weighted so that they correlate maximally with one dimension, but minimally with another. Thus dimensions that are not correlated are created.

[2] "Eigenvalues are a special set of scalars associated with a linear system of equations that are sometimes also known as characteristic roots" (Marcus and Minc, 1998: p. 144).

[3] Component loadings are the factor loadings in a factor analysis and are the weights correlated with a dimension. High component loadings are important in the definition of the dimension and variables with relative high component loadings on a dimension are strongly related.

3.11 ETHICAL CONSIDERATIONS

The research project maintained the ethical principles of participant autonomy, anonymity, confidentiality, justice and respect. Formal ethical approval was obtained for the study from the Human Genetics Departmental Research Committee and the Human Research Ethics Committee of the Faculty of Health Sciences prior to the commencement of the research (Rec/Ref: 213/2009) (Appendix 5).

The CRCGC, involved in the initial contact of the selected participants, explained the following during the first telephonic contact (Appendix 2):

- Purpose of the research;
- Participation was voluntary: participants were in no way coerced or persuaded to participate in the study;
- Withdrawal could take place at any time without jeopardising any medical services available to them or their families at the clinic or hospital;
- No discussion of the health or genetic status of other family members would take place.

When the consenting participants were contacted by the researcher, they were encouraged to ask questions or seek clarification of the study. In addition they were informed that they could decline to answer any of the questions in the interview schedule, request to have the tape-recorder switched off, or terminate the interview at any stage. All participants were 18 years of age or older, and legally competent to sign consent. Written consent was obtained prior to any interviewing, audiotaping or if any photographs were required. All the participants except one, who was illiterate, could provide written consent. For this participant, consent was provided by means of drawing a cross, witnessed by the CRCGC.

Every possible avenue for protecting the anonymity of participants was taken. The audiotapes were kept in a locked filing cabinet that only the researcher had access to and were destroyed as soon as the transcription process was complete.

A coding system was used to further protect the anonymity of the participants. The researcher assured the participants that the names and the information provided to her during the interview would be kept confidential, apart from the future publication in a scientific journal where names would not be used. Quotes were used to illustrate certain ideas or themes identified during the data analysis; however any details that could possibly result in the identification of the participant were not included.

If any anticipation of distress occurred during the recollection of the experiences, provision was made for referral to counselling services. The researcher ensured that she remained non-judgemental and that her body language did not convey disapproval if the information given by the participant was at odds with the genetic and medical knowledge or management recommendations.

While the purpose of the research interview is to gather data, it is commonly reported that interviewees seek advice or confirmation of the information given during the interview process (Patton 2002). As a genetic counsellor acting as a researcher, it was important that an ethical framework for dealing with such issues was established prior to the study to avoid her research role being taken over by a counsellor role. If necessary, and rather than intervene in the interview process, information booklets or follow-up sessions were arranged. This ensured that the researcher did not interfere with the data-collection process while maintaining the professional standard and code of conduct as a practicing genetic counsellor.

One of the critical, yet often neglected, aspects of research is the feedback of information obtained from the study to the community involved in the research project (Research Ethics and Environmental Health 2002). It was therefore ensured that the results and recommendations of the study were provided to the clinical and genetic team involved in the management of SA LS families as well as to the participants of the study. Participant feedback occurred after the completion of the research project and entailed either a written letter, or a home visit, depending on the preferences of the participant.

3.12 WEAKNESS OF STUDY

Any research study has limitations and cannot ever be comprehensively completed or include all the implications for practice (Holloway 2005). The limitations for this study included:

- The use of a cross-sectional design (Group A) meant that changes to the participant's experience of the surveillance aspects of the GESC could not be assessed over time. It was possible that certain views could have changed following further contact with the clinical/genetic team;
- Selection bias: individuals who chose to participate could be unrepresentative of the target population. Although all the individuals invited to take part in the study agreed to participate, individuals who did not attend the GESC to receive their genetic test result or who could not be contacted were not included in the cohort. They may not have attended because of dissatisfaction with the service;
- The use of interviews as the research tool was only capable of capturing the reconstruction of events as experienced by the participants, rather than how the interviewees may have behaved (Holloway 2005). It is acknowledged that the participants may have provided answers, which they thought, may have been appropriate rather than that of their true attitudes (Holloway 1997);
- As the interview schedule was based on the literature, genetic counsellor's opinion and input from the CRCGC, supervisor and co-

supervisors, the questions may have missed relevant points from the participants' perspectives;

- Minimal international literature and an absence of SA literature on certain aspects of the research study implied that a limited amount of data were available for comparison purposes;
- The participants were encouraged to provide the researcher with a true portrayal of their experience, without being corrected for their discrepancies. However it is acknowledged that the researcher's social class, gender, level of education and status as a genetic counsellor could have influenced the interview process.

3.13 STRENGTHS OF STUDY

- A large amount of rich data were produced through the use of interviewing enabling a detailed understanding of why people did what they did (Daly et al 1997);
- Each interview was conducted personally by the researcher in a venue of the participant's choice and in a language with which they were familiar and comfortable;
- Face-to-face interviewing was used which is known to improve response rates (Daly et al 1997);
- The use of a semi-structured interview as opposed to a structured questionnaire provided the participants with greater latitude to express their personal views and reasons for expressing certain facts and ideas. This enabled the researcher to focus on issues salient to the participants, seek clarification and explore or probe areas of interest;
- The analysis was an ongoing process, whereby the findings of the study could drive the sampling process as the study progressed;
- Certain questions used in the measurement scales were from other validated studies which increased the trustworthiness of the study;
- The use of a longitudinal design (Group B) meant that changes to the participant's experience of the genetic service, particularly the PT process, could be assessed in _eal-time'. This method minimised

recall discrepancies on the part of the participants, as they were asked to describe an event that was in the process of happening rather than something that occurred in the past and relied on memories interpreted over time;

- By tape-recording the interviews, the exact words of the participants were captured as the researcher could provide her full attention to what the participant said;
- Research bias: The researcher was conscious of her own assumptions and recorded her experiences and thoughts during each interview, in an attempt to overcome any potential bias associated with her subjectivity on the information obtained;
- The recommendations made by the participants were addressed and, where changes were requested, have been implemented or are in the process of being implemented into the GESC.

The presentation of the analysis, results/findings and discussion are combined in Chapter Four. This is customary in qualitative research (McMillan and Schumacher 2001) and subtitles are included to connotate the different findings. This facilitates the description and prevents unnecessary repetition of information, which distinct chapters for each component would require.

CHAPTER FOUR: ANALYSIS, RESULTS/FINDINGS AND DISCUSSION

CHAPTER FOUR

ANALYSIS, RESULTS/FINDINGS AND DISCUSSION

4.1 INTRODUCTION

This chapter provides the results/findings of the research study. The data obtained from each interview are presented and discussed in sections, with graphs and tables used to illustrate mutual relationships between items. As the research set out to evaluate the genetic and surveillance programme, data has been compared to the available literature, to highlight any similarities or differences. The outreach clinic has developed as a result of accommodating the socio-economic constraints of the individuals utilising the genetic and surveillance service. Particular focus has been directed at describing the participant population (including socio-economic and demographic backgrounds) and home environment to fully comprehend the effect of these factors on the psychosocial problems experienced.

In light of the volume of data that was collected, and to aid clarity, findings from Group A and Group B are presented and discussed separately.

- Group A – data gathered from individuals who were mutation-positive and on the surveillance programme for at least one year. The results of the evaluation of the surveillance aspects of the GESC are presented in Section 4.2 (page 120).
- Group B – data gathered from individuals who were in the process of undergoing PT are presented in Section 4.11 (page 209). The findings of the evaluation of the genetic testing and counselling programme of the GESC are discussed in this section.

The headings of each section are presented in the same format as the interview schedule. For ease of understanding, these two items should be

read together, however, the number and description of the items in the interview schedule do appear in the text.

Where applicable, direct quotes are included from the participants' interviews to provide the reader with greater insight into the information and to enhance the validity of the identified themes. If a participant's response required translation from Afrikaans to English, it has been indicated, after the quote. /…/ indicates that irrelevant material has been removed to aid clarity.

4.2 GROUP A - GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC (GESC)

Participants in Group A were all mutation-positive and had been involved in the surveillance programme for at least one year so that compliance with colonoscopic surveillance could be determined. To facilitate a more thorough evaluation of the GESC, individuals attending the established endoscopic centre (GSH) as well as those accessing the outreach component of the clinic were interviewed. While the GESC operates in the same manner whether occurring at GSH or on outreach, the participants reside in separate provinces in SA and come from very different socio-economic backgrounds. At times, and for comparison purposes, especially during the discussion of the demographic characteristics, data from Group A has been separated into information from the participants attending the hospital clinic (GSH) and those seen at the outreach centres. Mostly, however, data from the two clinics have been combined to identify trends within the group as a whole.

A total of 83 interviews were conducted to reach saturation, however, for three of these, the interviews were terminated (these three participants have been excluded from data analysis and do not appear in Table 7). One participant was experiencing emotional distress (unrelated to LS), the other suffered from a brain injury related to a previous accident, making it difficult to

recall information requested by the interview schedule. The third interviewee was intoxicated during two interview attempts and it was decided by the researcher and supervisors, to exclude him from the interviewing process.

Eighty-six percent (69/80) of the interviews were conducted in the participants' homes, 14% of participants (11/80) preferred to be seen in a private room in their local clinic or private office near their place of employment or residence.

As participants were selected for their experience of the surveillance service offered by the GESC, there was a varying time span from the time that genetic testing had occurred to the time when the interviews were conducted (Figure 7).

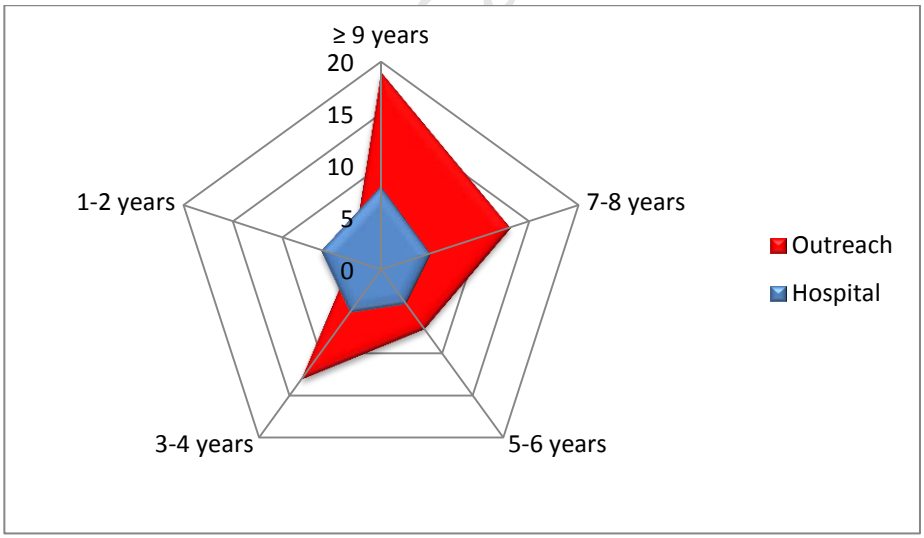

Figure 7: The number of years from the time of the genetic test to the research interviews (n=83).

4.3 DEMOGRAPHIC DATA AND PERSONAL HISTORY

Table 7 outlines the demographic data for participants from Group A and lists a comparison of the characteristics among participants who attend the outreach clinic and the hospital clinic (GSH). Fifty-two participants from the outreach clinic and 28 participants from the hospital clinic were included in the interviewing process.

Table 7: Sociodemographic characteristics of the study participants (n=80).

Participant characteristics	GESC (Outreach)		GESC (Hospital centre)	
	n=52	Percentage	n=28	Percentage
Gender				
Female	38	73 %	17	61 %
Male	14	27 %	11	39 %
Age (years)				
20-29	8	15 %	2	7 %
30-39	19	37 %	5	18 %
40-49	12	23 %	16	57 %
50-59	12	23 %	5	18 %
≥60	1	2 %	-	-
Ethnic group				
Mixed Ancestry	52	100%	24	86 %
White	-	-	4	14 %
Marital status				
Married/partner/relationship	33	63 %	18	64 %
Single/divorced/widowed	19	37 %	10	36 %
Home language				
Afrikaans	51	98%	19	68 %
English	-	-	6	21 %
English and Afrikaans	1	2 %	3	11 %
Province				
Northern Cape	52	100%	-	-
Western Cape	-	-	28	100%
Residential area				
Urban	10	19 %	27	96 %
Rural	42	81 %	1	4 %

The participants from both clinics were predominantly female (outreach 73%; hospital 61%), married (outreach 63%; hospital 64%) and spoke Afrikaans as a home language (outreach 98%; hospital 68%). The mean age of participants from the outreach clinic was 40.8 years (range, 21-70, SD=10.6) and the hospital clinic 43.1 years (range, 24-55, SD=7.6). Of these participants, 100% from the outreach clinic and 85% (24/28) from the hospital

clinic classified themselves as Mixed Ancestry. The four White participants (14%) were from the WC and attended the hospital clinic. As the general population of both the WC and the NC are mostly Mixed Ancestry (53.9% and 51.6%), the high incidence of this population group among the participants was not unexpected (Statistics South Africa 2005). In addition, the common founder mutation (C1528T mutation in MLH1), accounting for the majority of LS cases in SA, is observed exclusively in individuals of Mixed Ancestry (Goldblatt et al 1990; Ramesar et al 2000).

The marked difference noted between the two groups pertained to their residential location. Eighty-one percent of participants from the outreach clinic, living in the NC, occupied a rural dwelling (42/52), while 96% (26/27) from the hospital clinic, in the WC, were from an urban area. As the NC is one of the least developed provinces in SA, the high rate of rural residence is most likely due to population demographics in this area (Statistics South Africa 2005). Photograph 1 depicts a ‗matjieshuis' (reed hut dwelling). This type of housing structure is typical of the historic rural dwellings, seen in the NC.

Photograph 1: Typical ‗matjieshuis' (reed-hut) in Nourivier, Northern Cape.

Level of Education

Figure 8 compares the formal levels of education of the outreach to that of the hospital-screened group. Ninety-six percent (27/28) of participants from the hospital clinic and 88% (46/52) of participants from the outreach clinic completed junior school. In contrast, more participants from the outreach group completed secondary school than those from the hospital group (52% versus 39%). However, tertiary education was three fold higher (27% versus 9%) in the hospital group when compared to the outreach group. Nevertheless, both groups reported higher tertiary levels of education than that of the general population in their specific residential regions of the NC (6.1%) and WC (11.2%) (Statistics South Africa 2005). The mean years of education of the outreach group was 9.3 years compared to that of 12.3 years of the hospital group.

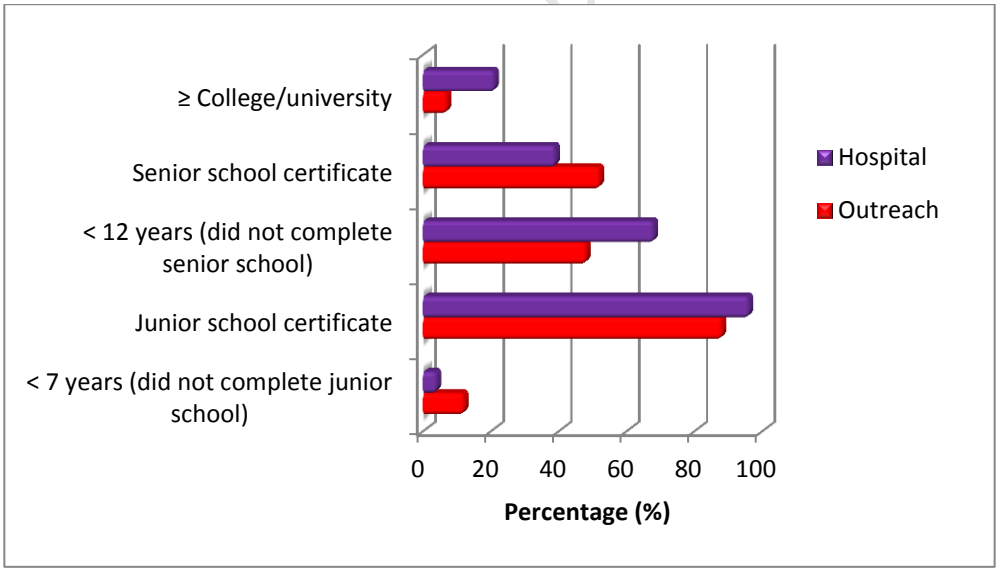

Figure 8: Level of education as defined by clinic (outreach versus hospital) among those participants aged 20 years and older.

Reasons for not completing schooling or tertiary education, reported on by the group as a whole, are presented in Table 8. It was not uncommon for both groups to have large families. Often the male or ‗brightest' child was selected to remain in school, while the daughters cared for the family or assisted with the household chores. Other families managed these difficulties by providing

minimal schooling for all their children rather than full schooling for a few. Those participants who indicated ‗other', cited ‗expulsion', ‗struggling or failing at school' and ‗having no friends at school' as the reasons for not completing their schooling.

Table 8: Reasons for not completing or continuing with schooling and/education (n=80).

	Frequency (n=80)	Percentage
No secondary/tertiary schooling in town/village of residence	10	8%
Social circumstances*	14	17.5%
Financial restraints of parent	20	25%
Preferred to start working/did not feel it was needed	11	13.75%
Financial/care support required as a result of the loss of the parent with cancer	8	10%
Other	6	7.5%

Data from the outreach and hospital groups have been collated.
*Social circumstances included pregnancy, concern for the political instability/rioting at the school (apartheid era), or joined a gang.

Employment

As can be seen in Figure 9, the rate of unemployment exceeded that of employment for participants in the outreach programme. A concerning 67.3% of participants (35/52) from the outreach clinic (NC) and 39.2% (11/28) from the hospital clinic (WC) were unemployed. The unemployment rate for participants from both clinics was significantly higher than that of the general population in the WC (18.6%) and the NC (13%) (Statistics South Africa 2005).

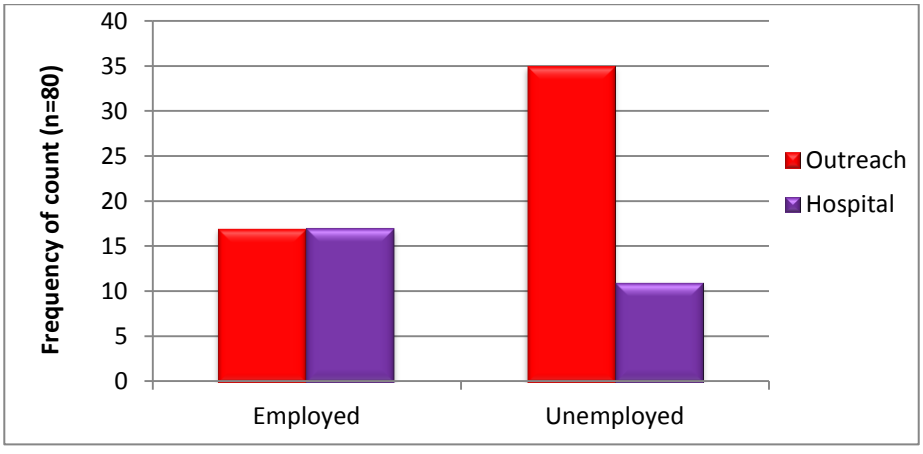

Figure 9: Comparison of unemployment rates for the outreach (n=52) and hospital (n=28) participants.

Reasons cited by participants, for being unemployed, are presented in Table 9. The down-scaling of the alluvial diamond mining operation at Kleinsee and the closing of the copper mine at Nababeep contributed significantly to the number of individuals who were unemployed in the NC and attending the outreach clinic.

Table 9: Reasons for unemployment (n=80).

	Frequency	Percentage
Care for family	5	6.3%
No work available	4	5%
Health-related	5	6.3%
Retrenched/business closed down	13	16.3%
Other family member/partner provides income	7	8.8%
On a social grant/pension	5	6.3%
Do not want to work or poor working conditions	2	2.5%
Other	6	7.5%

Data from the outreach and hospital groups have been collated.
'Other' refers to individuals who were unemployed as they had recently moved to a new area.

Occupation

The occupation categories among the employed population in SA have been defined as per the Census (2001) descriptions (Statistics South Africa 2005). The majority of participants from the hospital clinic were employed in the managerial, professional and semi-professional sectors (Table 10). This percentage was significantly higher than that of the general population in the WC (28.5% versus 22.2%). The majority of participants from the outreach clinic were employed in the lower income category of elementary occupations. It should also be noted that the percentage of participants, for each of the occupation categories, was significantly lower than that of general population of the NC.

Table 10: Occupation categories (n=80).

Occupation	Outreach (n=52)	NC population	Hospital (n=28)	WC population
Managerial, professional, semi-professional	7.7% (4/52)	23.5%	28.5% (8/28)	22.2%
Clerical, sales, service	7.7% (4/52)	22.3%	3.5% (2/28)	20.6%
Skilled agriculture, craft, operations	0% (0/52)	27.4%	3.5% (2/28)	23.3%
Elementary occupations	13.5% (7/52)	19.5%	25% (7/28)	29.2%

Income

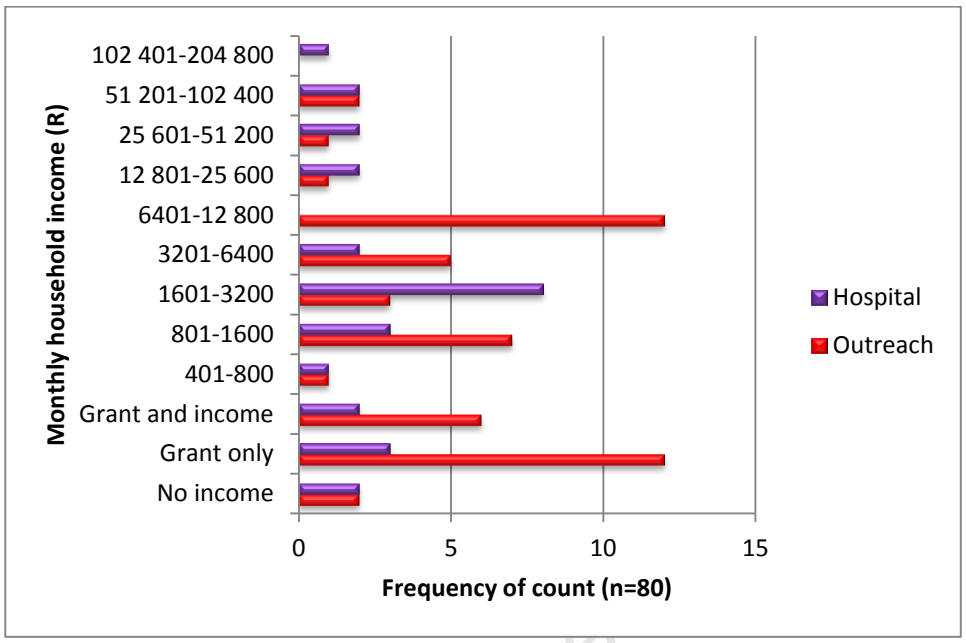

Figure 10: Comparison of the level of household income between the outreach (n=52) and hospital (n=28) group.

Figure 10 illustrates the discrepancy in the total monthly household income between the hospital and outreach groups. More participants from the hospital clinic were in a higher income bracket than those of the outreach clinic. The mean monthly income was R12 625 (USA$ 1 830) for the outreach group and R13 750 (USA$1 993) for the hospital group. A comparison to the general population was not made as statistics for monthly household income were not provided in the Census.

Nearly a third of participants (15/52) from the outreach group were solely dependant on social grants. Nine of the 15 participants received a pension (old age grant) from their original employer (De Beer‘s mining) following the closure of the Kleinsee mine and six participants received a state disability grant (DG). The DG, which was R1 080 (USA$ 157) per month, supported a mean of 5.5 persons per participant recipient. All participants with a DG (6/6) were from the Mixed Ancestry population group. It is interesting to note that the six individuals who qualified for this grant, did so as a result of a

resection/total colectomy following CRC. Applicants are eligible to apply for a DG if they were unable to work as a result of a physical/mental disability. A resection or total colectomy, however, does not typically lead to an individual being disabled or incapable of working.

Further information on the types of grants for which the households qualified, are given in Figure 11 and explained in Appendix 6. The grants held by the participants mentioned above are included in the count below (grants held by all households). For ten participants, more than one grant was received by the household.

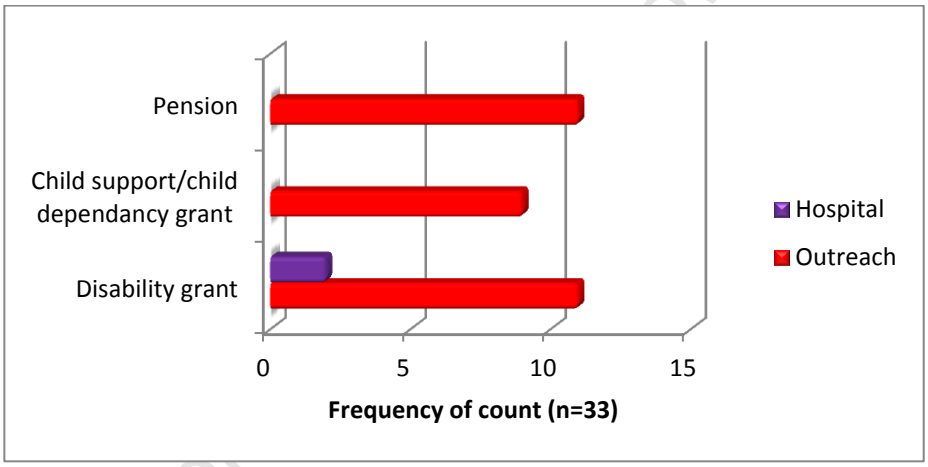

Figure 11: Type and count of social aid received from government.

The number of individuals dependant on the monthly household income is displayed in Figure 12. Three participants were from a household of 13 occupants (outreach group). The mean number of individuals per household was 5.8 for the outreach group and 3.1 for the hospital group.

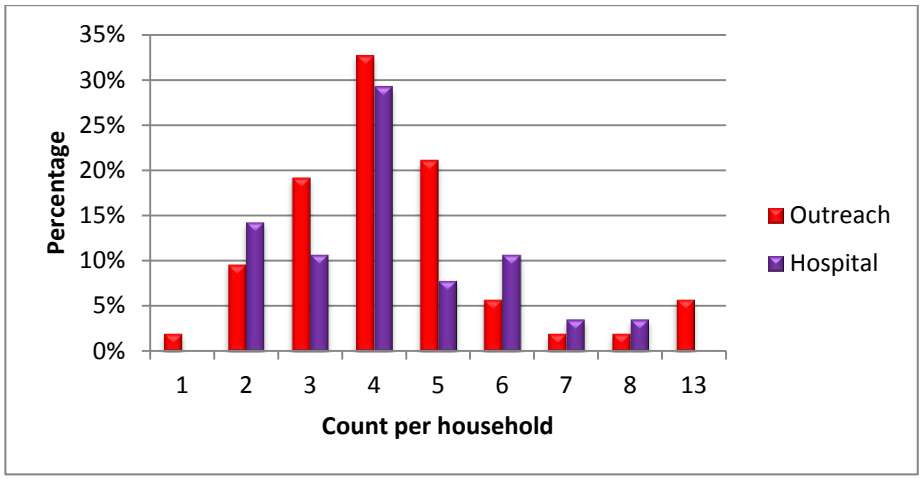

Figure 12: Comparison of the number of individuals per household of the outreach (n=52) and hospital group (n=28).

Family history and cancer profile

Table 11: Parental cancer history profile.

Affected parent	Participants		
	Male	Female	Total
Paternal	16 (21.6%)	20 (27%)	36 (48.6%)
Maternal	10 (13.5%)	27 (36.5%)	37 (50%)
Unknown	0 (0%)	1 (1.3%)	1 (1.4%)
Total	**26 (35.1%)**	**48 (64.8%)**	**74 (100%)**

Only one participant (1.4%), estranged from his parents, had been unable to identify whether or not he had a parent with a family history of cancer (Table 11). Ninety-one percent (73/80) of the remaining participants had an affected parent and 76.7% (56/73) of the affected parents had died following their cancer diagnosis. Thirty-four percent (27/80) of the participants had acted as a care-giver for a member of their family when they became symptomatic. Usually this would be a female participant (21/27). The type of cancer that the parent was affected with is illustrated in Figure 13. As would be expected, CRC contributed to the majority of cases (76%), while endometrial malignancy accounted for only 4% and more than one cancer type occurred in 6% of cases (CRC with endometrial, breast or prostrate cancer). Ninety-six percent of parents carried a MLH1 mutation. The remaining 4% (3/73) had a MSH2 mutation; two were affected with CRC and one remained unaffected.

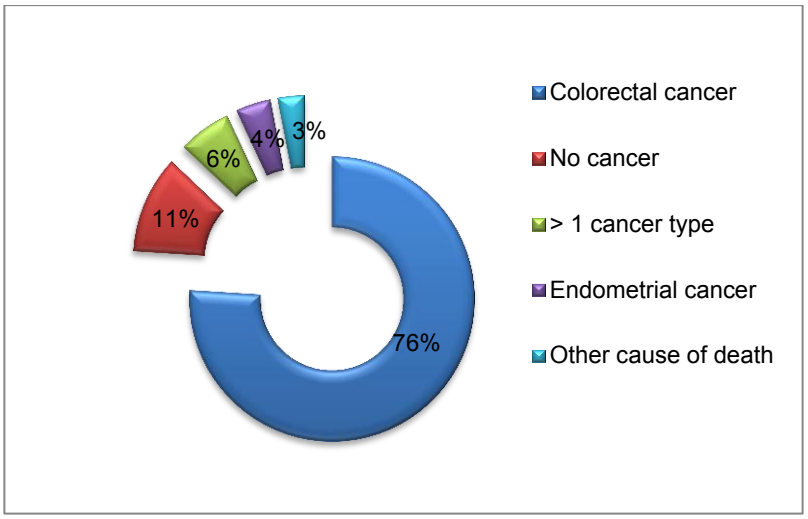

Figure 13: Type and frequency of the parental cancer of the participants in Group A.

Table 12 presents the age at which participants experienced a parent's cancer or cancer diagnosis. Most participants recalled a parental cancer when they were between the ages of 19-29 years (25%).

Table 12: Age of participant at parental cancer/cancer diagnosis.

Age at parental cancer diagnosis	Frequency	Percentage
0-6 years	10	12.5%
6-12 years	11	13.8%
13-18 years	11	13.8%
19-29 years	20	25%
≥30 years	15	18.8%
Parent not affected	4	5%
Did not know parent/could not recall when parent was diagnosed	9	11.3%

Some percentages may not add up to a 100% as a result of rounding-off.

First-degree relatives with colorectal cancer

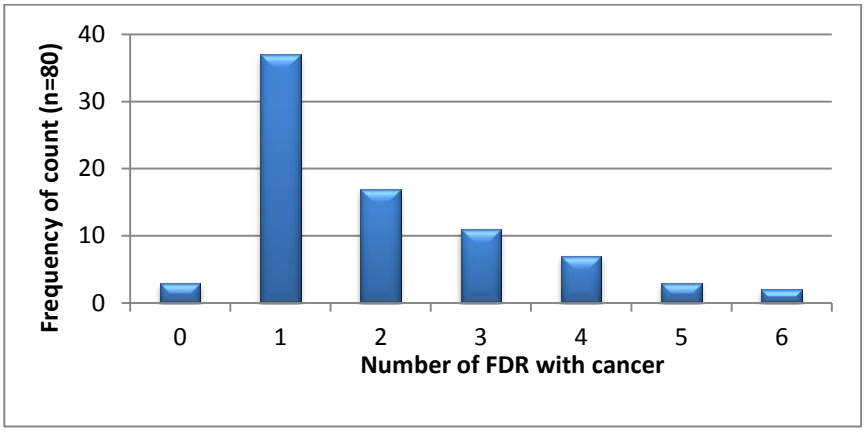

Figure 14: Comparison of participant's number of first-degree relatives (FDR) with colorectal cancer.

Thirty-seven participants had a single first-degree relative (FDR) with CRC (46.3%). The lowest number of FDR's with CRC per participant was zero (3/80). The highest count was six affected FDR's (2/80). The mean number of FDR with CRC among the 80 participants was two (Figure 14).

The number of siblings and children per participant is displayed in Table 13. The mean number of siblings and children per participant from the outreach group was 5 and 1.8 compared to that of the hospital group which was 6.1 and 2.4, respectively.

Table 13: Number of siblings and children per participant (n=80).

	Frequency of count									
	0	1	2	3	4	5	6	7	8	≥ 9
Siblings	9	3	7	12	13	10	12	10	3	1
Children	10	17	23	22	6	2	0	0	0	0

The incidence of LS in SA is unknown and the uptake of PT among the at-risk population has not been determined. Figure 15 and Figure 16 provide the uptake rate of PT among all FDR's (siblings and children) of the participants.

Figure 15 compares the uptake of PT among the siblings of participants attending either the hospital or outreach clinic.

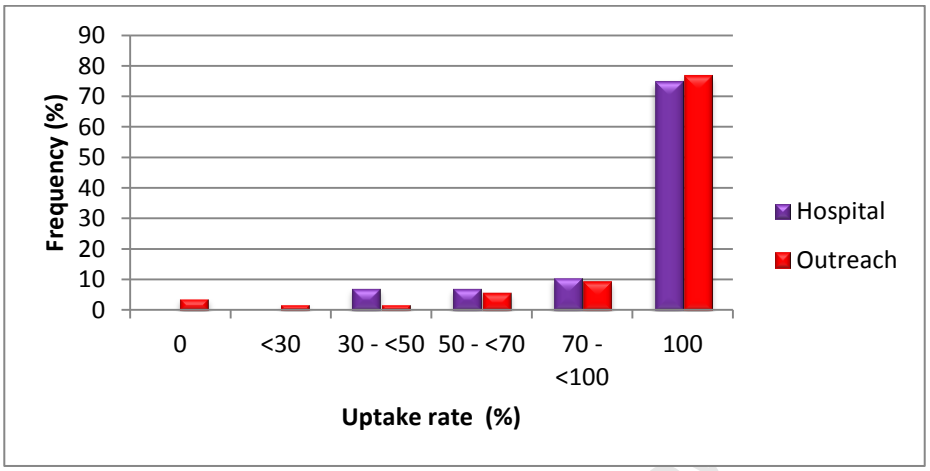

Figure 15: Comparison of uptake rate of genetic testing among the outreach and hospital participants' siblings.

The uptake rate among the participants' siblings was remarkably high with 97% (422/431) of the total number of siblings having undergone genetic testing. The number of participants, who illustrated a 100% uptake rate among their siblings, was comparable between the outreach and hospital groups (76% versus 75%).

Figure 16 depicts the comparison of PT uptake among the participants' children who were eligible to undergo genetic testing (over the age of 18 years). The uptake rate among the eligible children of the participants was high with 73.6% (64/87) of the total number of children undergoing PT. The number of participants who illustrated a 100% uptake rate, among all their eligible children, was considerably higher in the hospital group (32.1% versus 20.7%). A possible explanation for this could be that PT opportunities are more readily available in the hospital sector. PT, offered through the outreach clinic, is only obtainable during the period of the outreach trip, while PT through the hospital sector is accessible throughout the year.

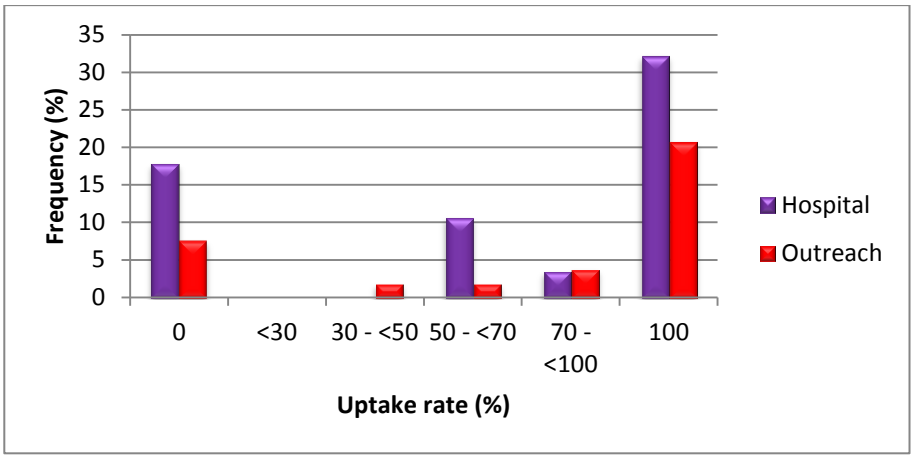

Figure 16: Comparison of uptake rate of genetic testing among the outreach and hospital participants' children.

Cancer profile

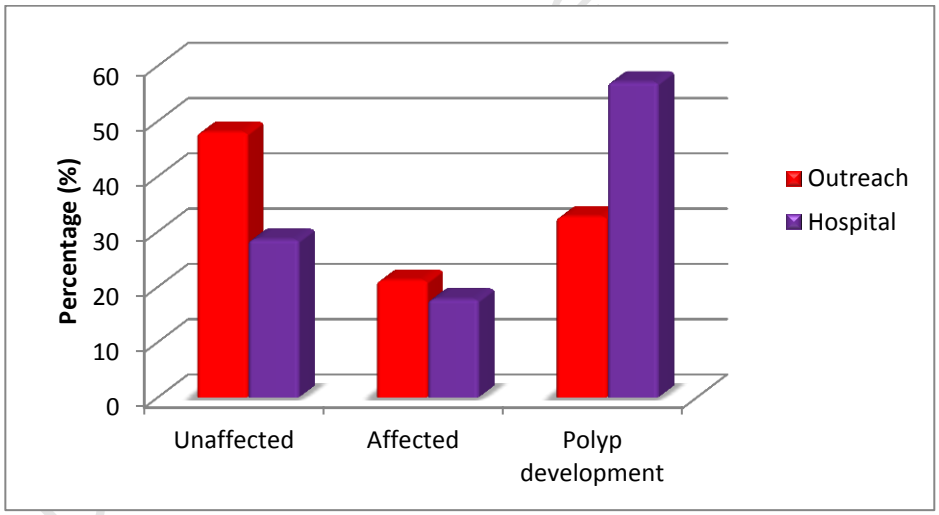

Figure 17: Comparison of cancer history of participants attending either the outreach or hospital clinic (n=80).

Marginally more participants from the outreach sector had been diagnosed with CRC (21.2%; 11/52) than in the hospital group (17.9%; 5/28). However, polyp development was greater in the hospital sector (57.1% versus 32.7%).

A summary of the characteristics of the 16 affected participants is provided in Table 14.

Table 14: Characteristics of the affected participants within Group A (n=16).

Participant (P)	Age at cancer diagnosis	Gender	Mutation	Site of cancer	History of surgery related to cancer	Predictive test (PT) / Diagnostic (D)	Affected with any other cancer		GESC	Adherence group∞
							Yes	No		
P3	50	M	MLH1	Descending colon	TC+IRA	D		x	Outreach	1
P4	47	F	MLH1	Caecum	TC+IRA	D		x	Outreach	2
P6	35	M	MLH1	Ascending and descending colon	Hemicolectomy	D		x	Hospital	2
P9	43	M	MLH1	Ascending	Hemicolectomy	D		x	Outreach	1
P15	52	F	MLH1	Transverse	TC+stomach wedge and block	PT		x	Outreach	5
P17	44	M	MLH1	Descending	Hemicolectomy	D		x	Outreach	3
P26	38	M	MLH1	Ascending and descending	TC+IRA	D		x	Outreach	1
P33	45, 50†	F	MLH1	Transverse, †duct carcinoma	TC+IRA, †R mastectomy	D	x		Outreach	2
P39	39, 49**	F	MLH1	Ascending, **descending	Hemicolectomy	D		x	Hospital	2
P42	44	F	MSH2	Sigmoid, descending colon	TC+IRA and small bowel resection	D		x	Hospital	2
P46	46	F	MLH1	Ascending	TC+IRA	D		x	Hospital	1
P50	39	F	MLH1	Rectal	Defunctioning loop colostomy	PT		x	Hospital	5
P65	29	M	MLH1	Caecum	TC+IRA	D		x	Outreach	2
P71	46	M	MLH1	Caecum	Right hemicolectomy	D		x	Outreach	2
P75	26	M	MLH1	Caecum	TC+IRA	PT		x	Outreach	2
P83	41	M	MLH1	Ascending, transverse and splenic	TC+IRA	PT		x	Hospital	5

TC+IRA – total colectomy and ileorectal anastomosis.
**Second primary colorectal carcimona.
†Breast cancer.
∞Adherence group refers to the number of missed colonoscopies as defined in Table 5 (page 90).

The mean age of the 16 participants who were affected with CRC was 41.5 years (range 26-52 years) (Figure 18). This is somewhat younger than that reported in the literature (Annie Yu et al 2003; Anwar et al 2000; Lynch and de la Chapelle 2003; Lynch and Lynch 2000) and the figure determined by Stupart et al (2009a) who investigated a SA LS cohort (44 years). Ten participants (62.5%) underwent a total colectomy with ileorectal anastomosis, five a hemicolectomy and one a defunctioning loop colostomy. Colorectal tumours in LS typically occur on the right side of the colon. However, the 16 participants diagnosed with CRC developed tumours throughout the colon and rectum. The majority (75%) of participants developed cancer prior to genetic testing. The mean adherence group (indicating compliance with screening guidelines) was 2.3, which is relatively compliant with recommended colonoscopic screening.

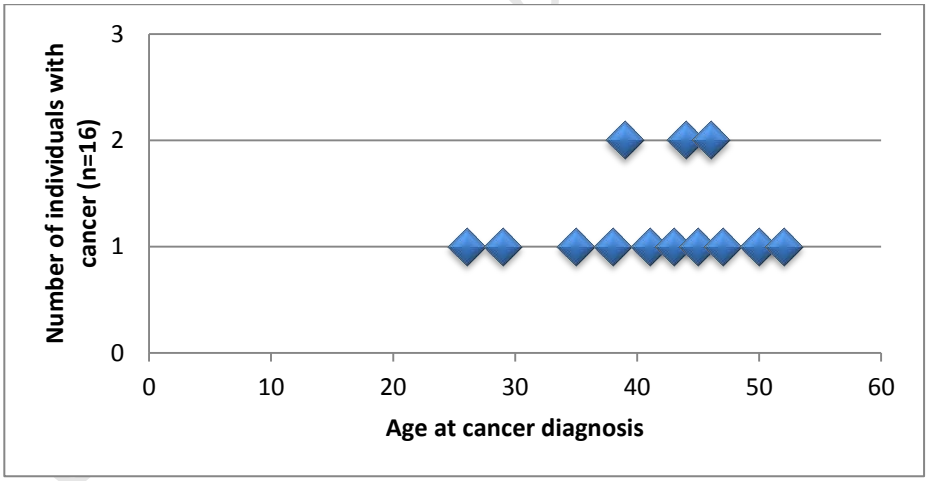

Figure 18: Age of onset of first colorectal cancer (n=16).

In this cohort, males presented earlier (mean 39.1 years) than females (mean 44.5 years). The younger age of onset in males, is however, a typical feature of LS (Abdel-Rahman et al 2006; Hampel et al 2005b; Lynch et al 1993b; Rodriguez-Bigas et al 1997).

4.4 KNOWLEDGE OF LYNCH SYNDROME

The level of knowledge of LS was measured with the Domanska et al (2009) scale. The hospital and outreach participants were grouped together to allow for the determination of overall knowledge and to identify areas least understood by the group as a whole. A description of each item has been included in Table 15 as it would have been too cumbersome to include in Figure 19.

Table 15: Description of items displayed in Figure 19.

Item	Description
B1a	CRC affects approximately 4-5% of all individuals in South Africa
B1b	Individuals who carry the gene for LS will definitely develop cancer
B1c	Individuals who do not carry the gene will never develop CRC
B1d	Females with LS have an additional risk of endometrial cancer
B1e	Females with LS have an additional risk of ovarian cancer
B1f	Colonoscopy is only useful in individuals with LS when there are bowel symptoms
B1g	Individuals with LS need regular colonocopies
B1h	Individuals with LS will pass the faulty gene on to 25% of their children
B1i	Tumour tissue can be used to diagnose LS
B1j	Blood samples can be used for genetic testing
B1k	The disease is most often inherited from the male side of the family

CRC-Colorectal cancer. LS-Lynch syndrome.

A comparison of correct versus incorrect responses to each item is shown in Figure 19.

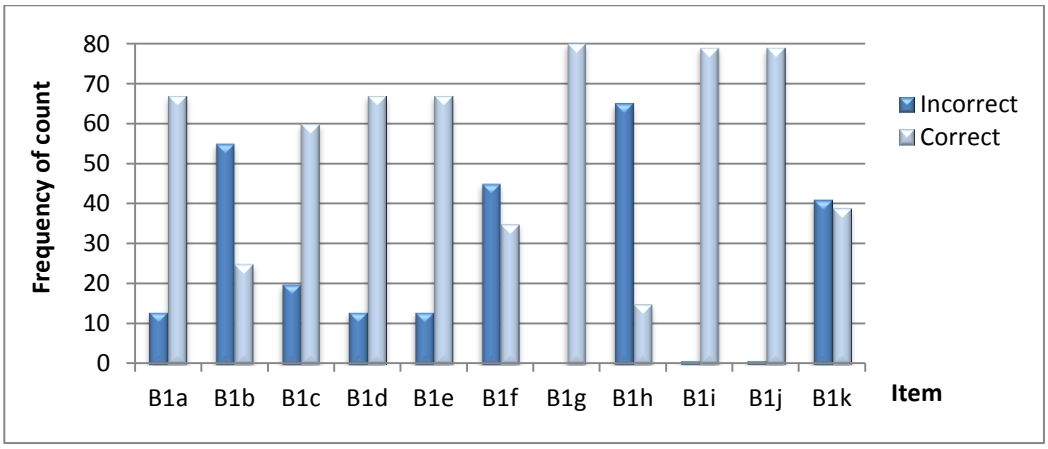

Figure 19: The number of correct answers per item of the level of knowledge questionnaire (n=80).

The mean number of correct responses was 6.5 out of 11 (range, 2-11). This is considerably lower than the median of 9 reported by Domanska et al (2009). However, consideration should be given to the fact that the Domanska study was conducted in a developed country (Sweden) where 81% of the participants had attended university versus 35% in the SA cohort.

The questions regarding the importance of regular surveillance, diagnosis and testing for LS had the highest frequency, with 100%; 99% and 99%, respectively, of correct answers. This is favourable as knowledge around the benefits of screening are associated with adherence to colonoscopic screening (Myers et al 1990). In contrast, knowledge about CRC related-risk and the genetic aspects of LS was less clearly understood: 69% (55/80) of participants felt that having the mutation meant that they would definitely develop cancer in their lifetime; 81% (65/80) incorrectly stated that the risk of passing on the mutation to their children was 25% (correct answer being 50%); and half (51%) thought that the mutation could only be inherited from the paternal side. While the recognition for regular colonoscopic surveillance was high (as previously mentioned, 99% answered this question correctly), only 44% (45/80) knew that the colonoscopy was beneficial before the presentation of symptoms. The majority of participants (67/80) recognised that LS predisposed females to an increased risk of endometrial and ovarian cancer.

Areas less clearly understood by the group are similar to those identified by Domanska et al (2009), who also found the genetic aspects of LS to be poorly understood by patients (Domanska et al 2009). In contrast to this present study, the Swedish participants failed to recognise the increased risk of gynaecological cancers.

Items B1g (individuals with LS need regular colonoscopies), B1i (tumour tissue can be used in LS diagnosis) and B1j (blood samples can be used for genetic testing) had over 99% correct answers and were excluded from

further analysis because of a lack of variance. Table 16 shows the number of participants with correct answers to the eight selected items (Ba, Bb, Bc, Bd, Be, Bf, Bh, Bk).

Table 16: The number of participants with correct answers to the eight items on the Domanska et al (2009) scale (n=80).

Correct answers	Frequency	Percentage
2	3	3.8%
3	15	18.8%
4	17	21.3%
5	20	25.0%
6	20	25.0%
7	4	5.0%
8	1	1.3%
Total	**80**	**100%**

The participants' main source of knowledge about LS was from the healthcare provider at the outreach/hospital clinic (Table 17). The distribution of 'knowledge' provided by the outreach/hospital clinic is Gaussian (normal distribution) peaking at knowing five of the eight items.

Table 17: Effects of the source of information on the level of knowledge (n=80).

		Source of information				
		Clinic†	Family	Internet	Other	Total
Knowledge score	2	1	2	0	0	3
	3	10	5	0	0	15
	4	15	2	0	0	17
	5	18	2	0	0	20
	6	14	5	0	1	20
	7	3	0	0	1	4
	8	0	0	1	0	1
Total		61 (76.3%)	16 (20%)	1 (1.3%)	2 (2.5%)	80 (100%)

† Clinic includes the outreach and hospital service.

The participant with the most accurate knowledge used the internet as a main source for locating information on LS. The individual was a 35 year old, female, of Caucasian ancestry and reported a high education (completed tertiary educating) and socio-economic status (income bracket 11). She was also only one of five participants to have the internet available as a resource.

The majority of participants did not seek further information on LS (Table 18). Of those participants receiving information from the outreach/hospital clinic, only 8.9% (7/56) looked to further sources to obtain more information. Forty-one participants (51.2%) had access to additional information resources. This included library books (33/80), magazines (3/80) and the internet (5/80). Terms used to search for information on LS included: _cancer' (1/7); _CRC' (3/7) and _HNPCC/LS' (3/7). Of interest, only seven of the 80 participants had heard of the term _HNPCC/LS'. This would have made obtaining additional information on the condition very difficult.

Table 18: Frequency of individuals seeking more information on Lynch syndrome per information source (n=80).

Source of information	Seeks more information on LS	Does not seek out information on LS	Total
	(n=80)	(n=80)	
Clinic†	5	56	61
Family	1	15	16
Internet	1	0	1
Other	0	2	2
Total	7	73	80
Percentage	8.8%	91.3%	100%

† Clinic includes the outreach and hospital clinic.

Only 35% (28/80) of participants acknowledged receiving a handout on LS from the GESC (information in the handout only covered surveillance preparation). Of these individuals, half (14/28) had retained the handout or could access it and 78.6% (22/28) had found it useful. Those six participants, who did not find it useful, reported that they had struggled to read the information as it was only available in English, which was not their home language.

Factors affecting knowledge

Collins et al (2000) reported a positive association between education and knowledge and noted higher knowledge scores among women compared to men. The present study does suggest that participants with a tertiary education had slightly higher knowledge scores than those with only a secondary schooling education (Figure 20).

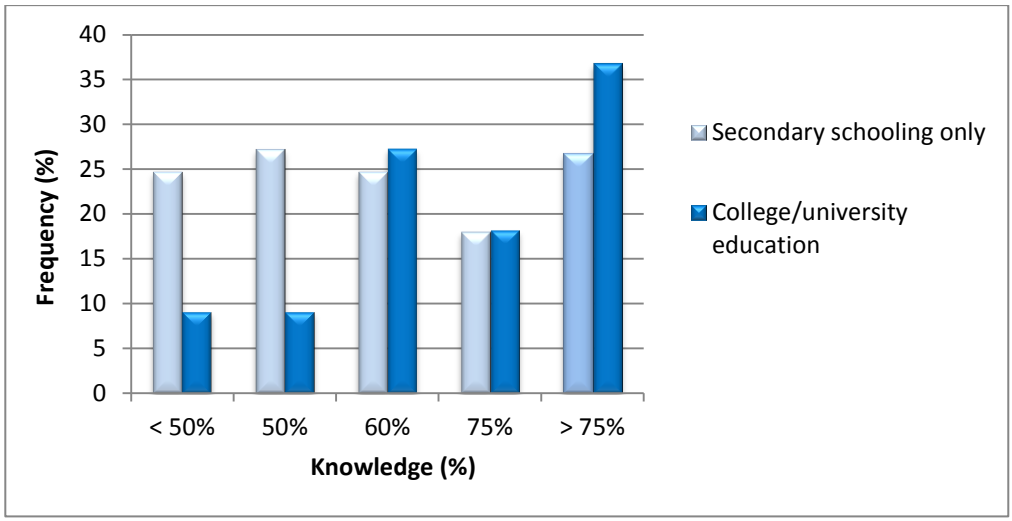

Figure 20: Relationship between education and knowledge (as measured by the Domanska scale).

However, the gender of participants in this study was unrelated to the level of knowledge of LS (Table 19).

Table 19: Knowledge score per gender of participant (n=80).

	Knowledge score							
	2	3	4	5	6	7	8	Total
Male	1 (4%)	5 (20%)	8 (32%)	3 (12%)	6 (24%)	2 (8%)	0 (0%)	25 (100%)
Female	2 (3.6%)	10 (18.2%)	9 (16.4%)	17 (30.9%)	14 (25.5%)	2 (3.6%)	10 (1.8%)	55 (100%)
Total	3 (3.8%)	15 (18.8%)	17 (21.3%)	20 (25%)	20 (25%)	4 (5%)	1 (1.3%)	80 (100%)

The means of the dependent variable (knowledge) and confidence intervals are shown in Table 20.

Table 20: The effect of gender on average knowledge score.

Dependent Variable: Knowledge				
Gender	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Male	4.560	0.269	4.025	5.095
Female	4.745	0.181	4.385	5.106

Furthermore, no relationship between adherence (Table 5, page 90) and knowledge, as measured by average knowledge within an adherence group, was found (Figure 21).

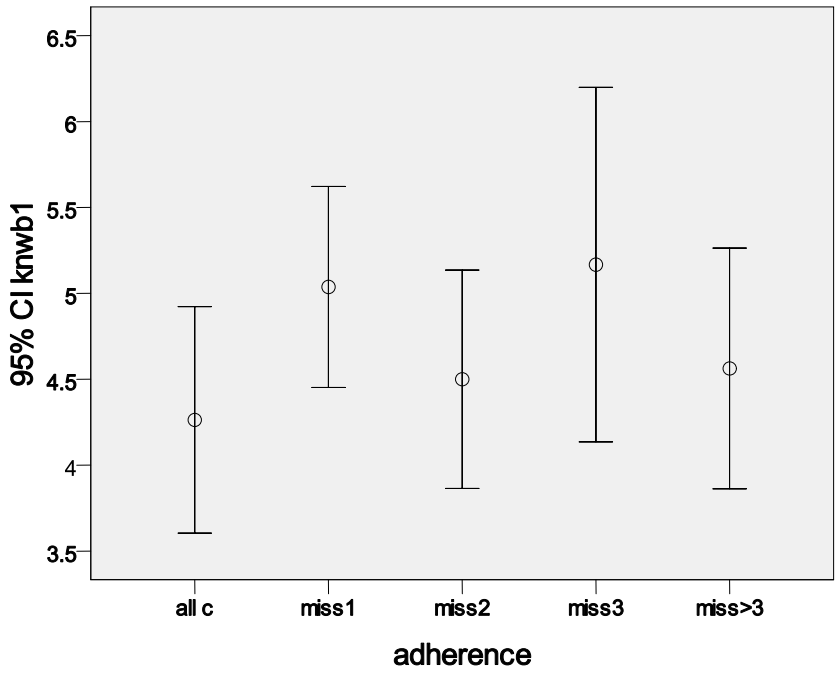

Figure 21: Level of knowledge per adherence group.

When length of time in the programme (calculated from the date the participant received their genetic test result) was considered with relevance to knowledge, a trend emerges and those participants with low knowledge appear related to the shortest exposure time in the programme. The exact length of time that the participants were involved in the programme is presented in Table 21.

Table 21: Classification of the number of years of subjects within the GESC.

Number of years in GESC programme	Code
≤ 3 years	3
>3≤8 years	2
>8-17 years	1

Table 22 illustrates that knowledge appears to increase with length of time in the GESC.

Table 22: Level of knowledge per number of years within GESC.

		Years in GESC programme			Total
		1	2	3	
Knowledge score (_/8)	Two	0	0	3	3
	Three	5	6	4	15
	Four	3	6	8	17
	Five	4	12	4	20
	Six	11	4	5	20
	Seven	4	0	0	4
	Eight	0	0	1	1
Total		27	28	25	80

1 = >8-17 years in programme.
2 = >3≤8 years in programme.
3 = ≤3 years in programme.

The means of the dependent variable (knowledge) falls within the lower and upper boundaries of the confidence intervals (Table 23).

Table 23: The relationship between length of time of subjects in the GESC and knowledge (n=80).

Dependent Variable: Knowledge				
Years in programme (prg)	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
1	5.222	0.249	4.726	5.718
2	4.500	0.245	4.013	4.987
3	4.320	0.259	3.804	4.836

Figure 22 illustrates that participants attending the GESC for a longer period were more knowledgeable about LS than those participants who had been involved in the surveillance programme for a shorter period of time.

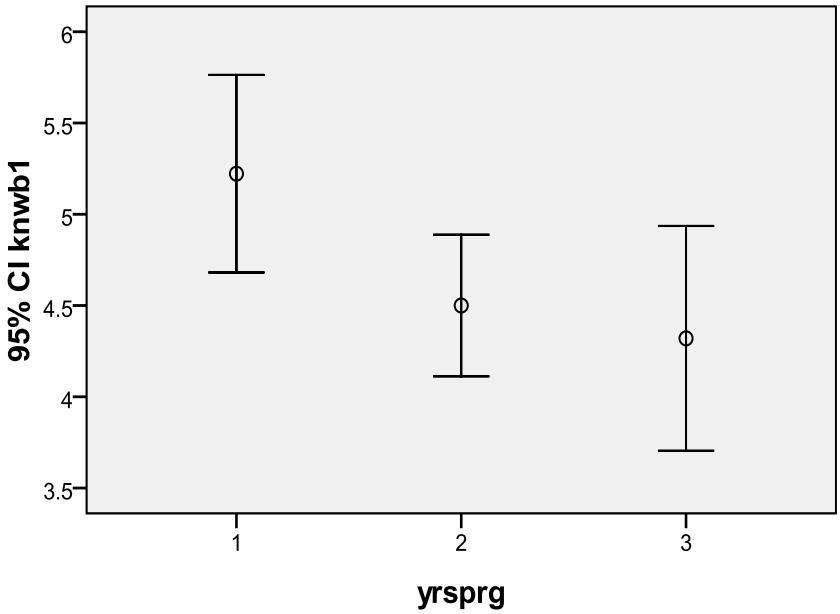

Figure 22: Average knowledge of subjects per number of years attending GESC.

1 = >8-17 years in programme.
2 = ≥3≤8 years in programme.
3 = ≤3 years in programme.

The trend was tested using Bonferroni Post hoc comparisons to control the false positive error rate associated with performing multiple statistical tests. It shows that only the difference (0.90) between knowledge of people shortly exposed and more extensively exposed to the program differs significantly from zero (the probability that there is no difference equals 4.2%).

Table 24: Bonferroni post hoc test (number of years within GESC and average knowledge).

Multiple Comparisons						
Knowledge (Bonferroni)						
(I) yrsprg	(J) yrsprg	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	0.72	0.349	0.126	-0.13	1.58
	3	0.90*	0.359	0.042	0.02	1.78
2	1	-0.72	0.349	0.126	-1.58	0.13
	3	0.18	0.356	1.000	-0.69	1.05
3	1	-0.90*	0.359	0.042	-1.78	-0.02
	2	-0.18	0.356	1.000	-1.05	0.69

Based on observed means. The error term is Mean Square (Error) = 1.677.
*The mean difference is significant at the 0.05 level.

Knowledge of Symptoms

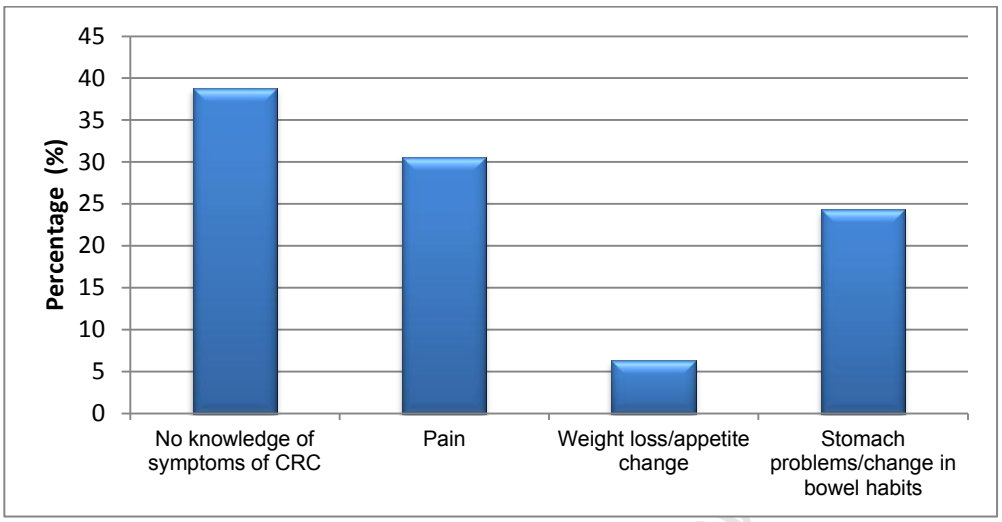

Figure 23: Knowledge of colorectal cancer symptoms among participants (n=80). CRC-Colorectal cancer.

While 61.2% (49/80) of participants could describe a symptom of CRC, it is of concern that 38.8% (31/80) had no knowledge of symptoms (Figure 23). Participants citing symptoms relayed that they had mentioned the various symptoms as a result of seeing a family member with CRC or having experienced it themselves. According to all the participants, no mention was made of symptoms during any information session.

Knowledge of inheritance

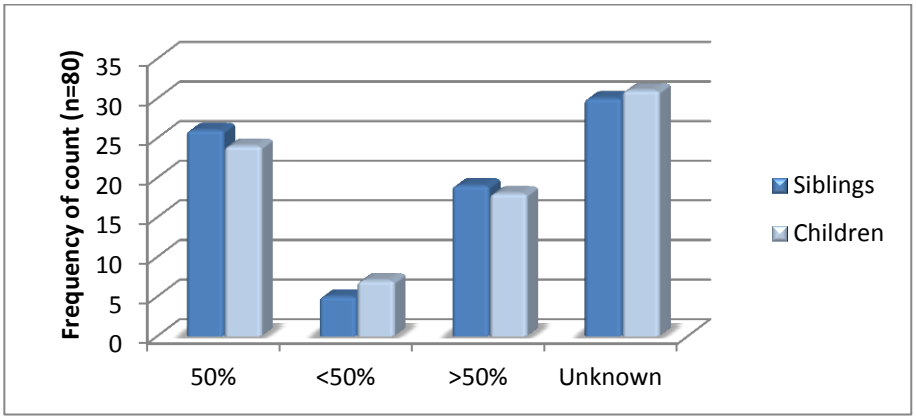

Figure 24: Recall of inherited risk to first-degree relatives.

Knowledge of passing on the genetic mutation was also assessed by asking participants about the inherited risk to their siblings and children (Figure 24). Forty-nine participants (61.3%) had heard about the 50% risk associated with autosomal dominant inheritance, but for 38.8% (31/80) of participants this was not clear. This is in contrast to Claes et al (2003) who illustrated a much higher correct recall (90%) among participants in their Belgian study. One reason for the low frequency of correct recall about inherited risk may be the fact that only 5/80 (6.3%) participants felt that they had discussed the inheritance of LS with their healthcare provider on a frequent basis. Sixty-nine (86.3%) participants reported on receiving information on inheritance at one point only, and only 5% (4/80) recalled that they had received this information more than once.

Fifty-eight percent (47/80) of participants recalled that the inherited risk to their children had been discussed with them, while 2.5% (2/80) felt that this discussion had provided them with limited knowledge on the risk. Four participants (5%) did not recall this being raised with them and 15 participants (18.6%) were told that their children had to be assessed, but they were unaware of the exact risk of transmission.

For those participants where this was discussed, feelings that were evoked have been highlighted in Table 25.

Table 25: Emotional response to hearing information of children being at risk for colorectal cancer.

Emotional response to inherited risk for children	Frequency of responses (_/80)	Quotes used to exemplify particular response category
Acceptance*	33	/../ well what can one really do about it, if it happens then it just happens and I will still encourage my children that at least something can be done, actually it is a privilege that we can go for these tests [colonoscopies]"(translated, male, 39 years). It is fine, really it is something beyond your control" (translated, female, 49 years). Look I thought it was an advantage knowing, cause you can do something about it prior to anything happening, if you know there is a chance that they could get it from you" (translated, male, 41 years). Well it was not really new news, you see this thing happening in your family, affecting grandparents, parents, cousin…I guess it is something that one just accepts, it's there/…/"(translated, female, 46 years).
Upset and/shocked	11	I prayed so much, you see you don't want this type of thing for your children, for their future - the fact that I had my blood test after I had my children and then had to find out that as I had it they could also have it, it was just…it was unexpected - you try and give them the best in life and then this comes along - you don't want this for your children! (translated, female, 49 years). Devastated - at one stage my wife felt that we should not have children /…/ (male, 43 years). It was difficult, and I was so upset and heart broken when I heard that my daughter stood a chance to develop…we all cried that day, it was so difficult to hear the news /…/ (translated, female, 37 years).
Sad	9	Well I actually felt quite sad, the fact that when I heard that I could inherit it from my father, that my life would change so drastically, and that I could not stop thinking about dying…well I wonder if they will go through the same thing if they were to inherit it from me" (translated, female, 37 years).
Guilty	4	/../ it was just horrible hearing that information, to give this type of thing to your children…" (translated, female, 27 years). A mother will always be heart broken knowing that she can pass it on to her children" (translated, female, 39 years).
Concerned	2	Initially I did not worry about that fact but when I had it happen to me, when I developed cancer I thought well if this happened to me it can also happen to my children and that, that is what worries me" (translated, male, 42 years).
Risk of transmission not discussed with participant/participant has no children	21	

*Reasons for acceptance are further discussed in the text.

Knowing that their children would accept the news of being at-risk and attend regular surveillance if required, acknowledging that surveillance could decrease the cancer risk, and realising that it was a family condition, were reasons given by 41.3% (33/80) of participants reporting ‗acceptance'. At times, acceptance was influenced by personal theories of inheritance, often linked to similar physical characteristics:

> ―I knew that out of my three children, [X] would be the one to have it…she is the one who looks most like me, is built like me and also you see, I was the most like my mother - it all makes sense, the three of us are also similar personality wise, and our traits /…/" (female, 53 years).

> ―My daughter, [X], was shocked when she found out she did not have it, the two of us are so similar, people even tell me she reminds them of me when I was younger, you see we had even told her to be prepared to find out that she would have it, it would be a bonus if she does not have it, but I told her she would more than likely have it, I mean I am incredibly happy that she does not have the risk that we all live with, but we were so sure…" (female, 49 years).

For four participants (5%), the decision to have children may have been negatively influenced if they had known about the transmission risk prior to starting a family. Six participants (7.5%) felt that it could potentially have impacted on their decision to have children. The large majority (66/80), expressed that it would not have made a difference, however, at times the decision involved extensive deliberation. The quote from P53 illustrates the extensive thought process and concern for the risk of transmission:

> ―My first thought was well obviously I can't have more children because I can't, uh, I can't risk giving this gene to someone else… it feels like a bit mean but then in the end I did have another child knowing that I could pass on the gene. I guess my thought was just that I was happy to be born, even though I have the gene - in the end it was a five year gap between the children as it was a big decision, can you really take it on yourself to pass on the gene, a 50% chance of the risk. I guess the main deciding factor was that it is not like I am passing on some kind of debilitating chronic condition, I am passing on a risk and a risk that is easily managed. My husband and I spoke about it many times and we decided that it was not a reason to not have kids" (female, 32 years).

The participant also highlighted her concern with the intentional decision to have a child while knowing that there was a 50% chance of transmission:

~~/~~../ but I am sure that [X] will be okay with her risk as I did not know about the gene when I had her, I did not know that I could potentially pass anything on to her, but with [Y] I did know there was a chance and I'm sure that if she does have the gene she may well turn around one day and say: How could you do this to me!".

Perceived lifetime risk of developing CRC

Table 26: Perceived lifetime risk of developing colorectal cancer.

Category	Frequency	Percentage
Inevitable (100%)	6/80	7.5%
Very high (≥75%≤100%)	33/80	41.3%
50% risk	7/80	8.7%
Low	28/80	35%
Uncertain of lifetime risk	5/80	6.3%
Adjusted due to specific familial characteristic	2/80	2.5%

Bottorff et al (1998) suggest that risk-related information is not capable of being presented within a vacuum and a subjective interpretation is most likely to occur, framed by social and familial meanings, which may be inconsistent with the actual genetic risk (80% lifetime risk of developing CRC). Six participants (7.5%) felt that CRC development in their lifetime was inevitable. It is of interest to note that these participants had all lost a parent to cancer, however, no clear association existed between this view (of cancer being inevitable) and adherence to colonoscopic screening. Of the six participants who expressed that their lifetime risk of developing CRC was 100%, three were adherent (Group 1 and Group 2) and two were non-adherent (Group 5).

Many participants referred to their perceived risk in a qualitative form rather than an exact numerical risk, and both are included in Table 26. The majority of participants viewed their personal risk as high (ranging from ≥75%), while 35% (28/80) of participants expressed their risk as ‗low'. Reasons cited for the latter included: having had a hemicolectomy/total colectomy, attending for regular surveillance, being beyond the age that cancer affected parent/family member with CRC, being a different gender to family members who had cancer and believing that cancer gets less severe with each successive generation:

‘Lower than previous generation as the cancer does not seem to affect everyone as badly any more” (translated, female, 53 years).

‘I think it is high as I am a woman and it comes from the women in the family and therefore it will be greater for me” (translated, female, 33 years).

4.5 GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC

The approximate travel time and type of transport to the outreach/hospital GESC is listed in Table 27. Seven of the 80 participants had never attended any form of surveillance and were therefore excluded from further analysis.

Table 27: Transport and travel time to Genetic and Endoscopic Surveillance Clinic (n=73).

Travel time to GESC	Type of transport	Frequency (n=73)	Percentage	Total
Minutes	Walk	7	8.8%	
	Private	1	1.3%	
	Public	1	1.3%	
	Free hospital ambulance	1	1.3%	10
< 1 Hour	Walk	1	1.3%	
	Private	11	13.8%	
	Public	3	3.8%	
	Free hospital ambulance	2	2.5%	
	Other	2	2.5%	19
1 Hour	Private	7	8.8%	
	Public	3	3.8%	
	Free hospital ambulance	11	13.8%	21
< 2 Hours	Private	3	3.8%	
	Free hospital ambulance	5	6.3%	8
> 2 Hours	Private	4	5%	
	Public	2	2.5%	
	Free hospital ambulance	9	11.3%	15

Data from the outreach and hospital clinic are presented together. ‘Other‘ indicates hitching a ride took place.

More than 50% (44/73) of the participants attending for surveillance at the GESC, travelled ≥ one hour to the clinic. The most utilised form of transportation (38.8%) was by ‘free hospital ambulance‘, followed closely by ‘private‘ transport (35.7%) which included the participant‘s own vehicle or the use of a family/friend‘s vehicle.

Participants attending the GESC have access to free transport by means of ambulance services arranged by their local primary clinics. Eleven participants (21.2%) from the outreach clinic incurred costs for transportation, as they made use of their own private transport, preferring this to that of the ambulance service. The concern with this service is conveyed by the following extracts:

> "…/ the ambulance never stops to allow for toilet breaks" (female, translated, 33 years).

> "We drove for over four hours to get there, it was terrible, the driver would not stop if you needed to go…the road is very dangerous and [X] drove like a maniac to get us there, it was a terrifying trip" (female, translated, 43 years).

Table 28 shows the relationship between missed appointments and type of transport and travel time per participant. Participants with the most missed appointments had travelled for approximately an hour.

Table 28: Travel time and mode of transportation for participants attending for surveillance but missing one or more colonoscopies (n=54).

Time to GESC	Mode of transportation	Adherence group				Total
		Missed 1	Missed 2	Missed 3	Missed >3	
Minutes	Walk	2	1		0	3
	Private	1	2		0	3
	Public	0	0		0	0
	Total	3	3		0	6
< 1 Hour	Private	4	3		1	8
	Public	1	1		0	2
	Free hospital ambulance	2	0		0	2
	Other	0	0		1	1
	Total	7	4		2	13
1 Hour	Private	1	2	1	1	5
	Public	1	1	0	1	3
	Free hospital ambulance	6	2	1	1	10
	Total	8	5	2	3	18
< 2 Hours	Private	0			1	1
	Free hospital ambulance	4			0	4
	Total	4			1	5
>2 Hours	Private	2		1	0	3
	Public	2		0	0	2
	Free hospital ambulance	1		3	3	7
	Total	5		4	3	12

Data from the outreach and hospital clinic are presented together and data from Adherence Group 1 (attended all colonoscopies) has been excluded from analysis. 'Other' indicates hitching a ride took place.

Patients travelling ≤ one hour who missed most appointments were using ‗private' transport (61.5%; 8/13). Of all the participants, 28.8% (21/73) travelled for ≥ one hour, missed most appointments and used the free hospital transport (Table 29).

Table 29: Travel time and adherence group for participants utilising free hospital transport (n=21).

Transport	Travel time	Adherence				Total
		Missed 1	Missed 2	Missed 3	Missed >3	
Free hospital ambulance	1 Hour	6	2	1	1	10
	< 2 Hours	4				4
	> 2 Hours	1		3	3	7
Total		11		4	4	21

Table 30 shows the level of knowledge on LS for the 21 patients who missed appointments using free hospital transport with a travel time of ≥ one hour. Non-adherence (missed appointments), however, was not only confined to the individuals with a low-knowledge score.

Table 30: Knowledge of participants using free hospital transport (n=21).

Knowledge score (_/8)	Frequency	Percentage	Cumulative Percentage
2	1	4.8%	4.8
3	2	9.5%	14.3
4	4	19%	33.3
5	10	47.6%	81.0
6	3	14.3%	95.2
7	1	4.8%	100.0
Total	21	100%	

Most of these participants, using free hospital transport, and who missed appointments were female (Table 31). This may be a reflection of the high number of females within the cohort (68.8%). However, the females within this selected group were less compliant (missed more than three appointments) than their male counterparts (missed two appointments).

Table 31: Gender cross-tabulated with adherence and travel time.

Gender			Travel time			Total
			Hour	<2 Hours	>2 Hours	
Male	Adherence group	Missed 1	1	1		2
		Missed 2	1	0		1
	Total		2	1		3
Female	Adherence group	Missed 1	5	3	1	9
		Missed 2	1	0	0	1
		Missed 3	1	0	3	4
		Missed >3	1	0	3	4
	Total		8	3	7	18

The employment status and age distribution amongst the 18 females using free hospital transport is presented in Table 32. Most of these females who missed appointments were ≥ 50 years and of Mixed Ancestry.

Table 32: Employment status per age group (n=18).

		Employment status		Total
		Yes	No	
Age	20-29	0	1	1
	30-39	2	3	5
	40-49	1	4	5
	≥ 50	1	6	7
Total		4	14	18

The age group and number of missed appointments for these participants (18 females) are compared in Figure 25. The higher age groups were over-represented in the columns with the most missed appointments (> three missed appointments).

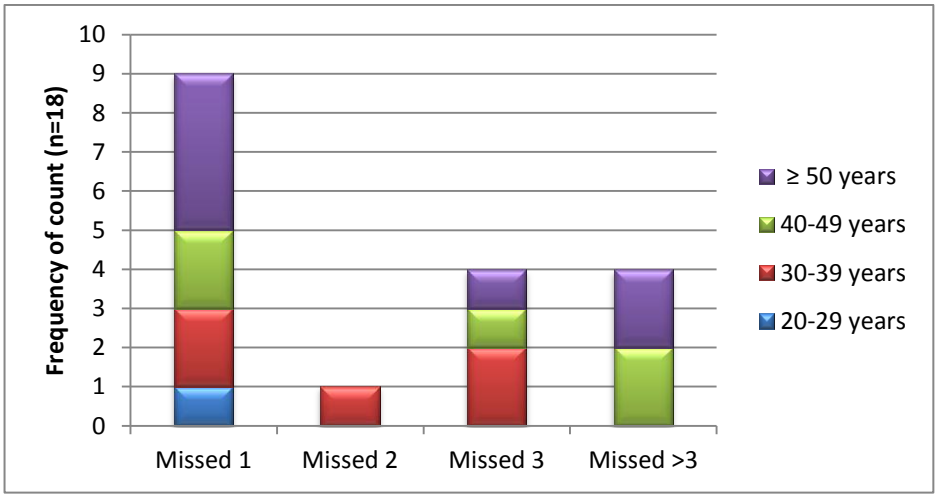

Figure 25: Frequency of missed appointments per age group.

Surveillance

Ninety-three percent of participants (74/80) had been for colonoscopic surveillance. The number of participants within each adherence group are listed in Table 33. Fewer than 25% of all participants obtained 100% adherence.

Table 33: Adherence to recommended screening guidelines (n=80).

Adherence group	Attendance	Number of individuals interviewed	Percentage
1	None missed	19	23.8%
2	1 Missed	27	33.8%
3	2 Missed	12	15%
4	3 Missed	6	7.5%
5	>3 Missed	16	20%
Total		80	100%

Participants were questioned extensively regarding the frequency with which they attended/missed their surveillance appointments. This self-reported adherence was compared to actual adherence as calculated from the database records (Figure 26).

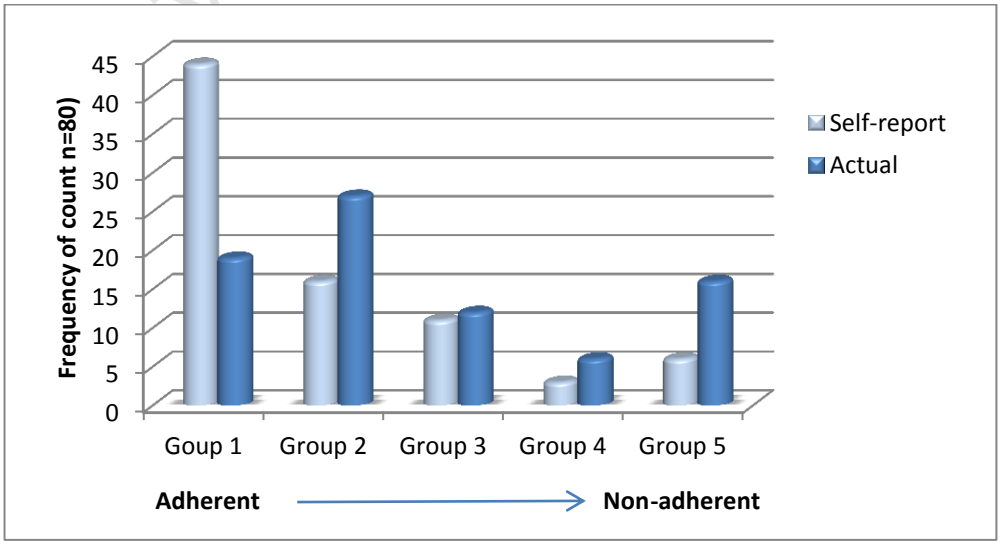

Figure 26: Self-reported adherence versus actual adherence.

The greatest discrepancy between actual and self-reported compliance can be seen in Group 1 (no missed appointments). More participants classified themselves compliant with screening guidelines than the actual number of participants in Group 1 (44 versus 19). It is also interesting to note that non-adherence was under-represented in Group 4 and Group 5, which are representative of greater non-compliance. Self-reported adherence was half of the actual adherence in Group 4 (6 versus 3) and only six of the 16 participants correctly selected their adherence in Group 5 (missed >3 surveillance appointments). Thus compliance rates based on self-report are not consistent with those rates obtained from medical records (reflecting actual adherence). This confirms the findings of the only other study which compared self-reported compliance to objective compliance (Bleiker et al 2005). This present finding and that of Bleiker et al (2005) suggest that over-estimation of compliance may occur in studies considering only self-reported screening behaviour (Ersig et al 2009; Hadley et al 2004; Halbert et al 2004; Stoffel et al 2003).

When participants were asked how often they thought they should go for colonoscopic screening, 78.8% (63/80) knew that this had to be on a yearly basis, 8% (6/80) responded that this should occur every two years and 6% (5/80) that screening should take place every two years prior to the age of 30 years, and annually thereafter. Of concern, is that 6% (5/80) did not know how often colonoscopic surveillance was required and 3% (2/80) of participants mentioned that they only had to attend for surveillance when they were requested to do so by their healthcare provider, or if they were experiencing symptoms. Only three of the seven participants who had never been for a colonoscopy did not know the frequency of required screening. The majority of these seven individuals were female (85.7%), of Mixed Ancestry and attended the outreach sector of the GESC (Table 34).

Table 34: Demographic data on the seven participants who had never had a colonoscopy.

Participant	Gender	Age (years)	Ancestry	Affected (Yes/No)	Clinic
P19	F	24	MA	No	Outreach
P37	F	42	MA	No	Outreach
P49	F	38	MA	Yes	Outreach
P60	F	27	MA	No	Outreach
P62	F	33	MA	No	Outreach
P68	F	40	MA	Yes	Hospital
P83	M	40	MA	Yes	Hospital

MA - Mixed Ancestry.

Remarkably, 87% (20/23) of participants who had a total colectomy were aware that they required yearly flexible sigmoidoscopies.

Surveillance experience

The experience of having regular surveillance was determined by asking the participants about various stages of the screening process. This included: colon preparation (drinking either a low- or high-volume bowel cleansing agent), accessibility of toilet facilities and the colonoscopy procedure. The broad categories defining this experience are identified in Table 35 and described in greater detail in the text.

Table 35: Personal experience of surveillance (n=80).

Personal experience of surveillance	Frequency	Percentage
Colon preparation		
Unpleasant	39/80	48.8%
Pleasant	27/80	33.8%
Ambivalent	2/80	2.5%
Type of prep makes a difference	5/80	6.8%
Never had a colonoscopy	7/80	8.8%
Toilet facilities		
Outside toilet	15/80	18.8%
1 household toilet (indoors)	43/80	53.85
> 1 household toilet (indoors)	22/80	27.5%
Procedure		
Fine	27/80	33.85
Uncomfortable	13/80	16.8%
Painful	23/80	28.%8
Anxiety prior to colonoscopy	4/80	5%
Other	2/80	2.5%
Never had a colonoscopy	7/80	8.8%

For thirty-nine participants (48.8%), the preparation procedure was experienced as unpleasant and described as the most difficult part of the screening process. More females (52.7%) than males (40%) found drinking the bowel cleansing agent distasteful.

> –Ohhh-it's not nice, the minute I drink it I am nauseous and I immediately throw up from it…it's horrible" (female, translated, 37 years).
>
> –It tastes terrible, but I just have to drink it, it makes me so full and causes my stomach to feel incredibly hard - and then sometimes it comes out from the top not only the bottom" (female, translated, 54 years).
>
> –To drink that...it's very difficult, the test [colonoscopy] is actually so easy compared to drinking the prep" (female, translated, 34 years).

However, over a third (27/80) viewed it as a pleasant experience and described it as:

> –I drink it as if it is water - it goes down well" (translated, female, 58 years).

Seventy-four percent of individuals (20/27) with a positive preparatory experience were compliant with screening guidelines (having missed none or only one appointment). Only two participants were ambivalent about the experience and five participants (6.3%) felt that the type of preparation mixture made a difference. Either a low- or high-volume bowel cleansing agent was preferred:

> –That one packet, [X], it really made me feel sick, but the other one, [Y], that was much better, it was a lot easier to do with the other one" (female, translated, 37 years).
>
> –The prep has gotten better since I have had the sachet with a glass of water and not litres of it - makes it so much easier" (female, 53 years).
>
> –./../ by far the worst bit, that stuff tastes so awful and really hard to get it down, I've had, I think seven colonoscopies and it seems to be different every time – the one time it made me really sick, I had shivers and I felt really nauseous but the last time it was a ginger flavoured concoction and it was not as disgusting as usual - the lemon that's the worst, with the ginger the whole experience was fine, it was nothing, but that lemon one - that's the one that I felt feverish with" (female, 35 years).

Effective preparation is crucial to the visualisation of the bowel lining (to detect polyps or cancer) during a colonoscopy (Järvinen et al 2000). Factors affecting compliance with preparation include the volume of the preparation liquid consumed (McCann et al 2009) and, in this study, the preference for a specific type of preparation.

Amenities

Gaining information on the accessibility and standard of toilet facilities is instrumental in understanding the preparation process, particularly in a developing country where these amenities are usually below standard. Photograph 2 depicts a typical ‗outside toilet' in Buffelsrivier, a rural village in the NC (Figure A). Photograph 3 illustrates the abysmal living conditions in Nourivier. The yellow bucket in this picture is used as a makeshift toilet at night and the individuals from this household have access to their neighbour's outdoor toilet during the day.

Photograph 2: Outside toilet in Buffelsrivier, Northern Cape.

Photograph 3: Makeshift bucket toilet in Nourivier, Northern Cape.

As 81% (42/52) of participants from the NC were from a rural dwelling, certain individuals only had access to a single toilet that was located outside the house. P70 describes how an ‗outside toilet' is built and the difficulties in acquiring an indoor toilet:

> ―An outside toilet is basically a hole in the ground - the gravel and bricks are laid in the hole and then a slab of cement is poured over it. The draining process happens as a result of the spaces between the bricks, and it sort of filters into the ground /…/ to have an inside toilet, the municipality has to lay down water pipes - it is quite a difficult thing to do and they must also approve your plans first" (female, translated, 58 years).

Almost 25% (15/80) of participants had only an ‗outside toilet'. This exceeds the figure of the general population where 10.1% of individuals in the WC and 11.2% of individuals in the NC report bathroom facilities to only include an outside, non-flushable, toilet (Statistics South Africa 2005). More than 50% of the participants (43/80) had access to a single indoor toilet which was shared with other family members or acquaintances and 27.5% (22/80) of participants had access to more than one indoor toilet. The difficulties associated with the colon preparation, particularly for participants using an ‗outside toilet' are highlighted:

> "Look the most difficult part is if you have to venture out at night to go to the toilet /…/ the last time I spent the whole evening outside and it was bitterly cold" (female, translated, 56 years).

> "It was just too cold the last time, so I had to go in a bucket inside the house" (female, translated, 22 years).

> "My sister has a toilet inside the house, when I drink the prep I stay with her but there are three people living with her so at times you have to hold out for the toilet" (female, translated, 35 years).

Not having an indoor toilet meant the preparation process was difficult to complete and in a few cases the cause for non-adherence to screening guidelines:

> "/…/ and before everything was so difficult, I mean we had an outside toilet, we had to drive for four hours on the ambulance to get there and it was a constant need to go to the toilet, which you couldn't…it was then that I decided I would rather go when I could sort out my own amenities – a toilet in the house, then I know I do not have to go outside at night - its cold and unpleasant. I now have everything in my house, the loo is inside and I have my own transport - so if I have to go now, I go. There is nothing else standing in my way" (female, translated, 43 years).

Colonoscopy

It is encouraging to note that 50% (40/80) of the participants viewed the colonoscopy as 'fine' or only 'uncomfortable'.

> "It is not a problem, I actually enjoy it, I can see my colon on screen, it is so interesting to see your insides like that" (female, translated, 37 years).

> "It is not that bad, I always go first to show the new people that it is okay" (female, translated, 58 years).

> "Not a problem, I do it without sedation every time" (male, translated, 35 years).

> "It's not sore, maybe a bit uncomfortable, especially near the turn of the colon, but I prefer to watch it on the screen, so that I can see if I am healthy or not - then you know /…/" (male, translated, 40 years).

Participants reporting positive experiences were more likely to be adherent to screening recommendations. Seventy percent of these individuals,

expressing a favourable experience, were from Group 1 (all recommended colonoscopies attended) or Group 2 (missed only a single colonoscopy). This finding, of greater adherence among individuals with a positive experience of colonoscopies, has been reported elsewhere (Gili et al 2006).

Often, the experience of pain associated with the procedure was operator dependant:

> "The colonoscopy is nothing, if Dr [X] does it, it is nothing, I must say that I have been hurt by others - they just don't listen to you. I have probably gone for more colonoscopies than some doctors have even done before, so shouldn't I get a say? /…/ Dr [X] knows I know as much about the procedure as can be known, so Dr [X] listens to me, I think it is Dr [X] technique as well as that, that makes a difference to the experience" (female, 53 years).

> "I will never have another colonoscopy if Dr [X] leaves" (female, 32 years).

For some participants, the initial procedure may have been painful, however the level of discomfort was found to decrease over time:

> "It has always gotten easier, the first time was quite sore, but I have been going for more than six years now and it's actually quite nice the last few times" (female, translated, 38 years).

> "It gets better with every year – I did not even feel anything with the last two, I even asked the doctor if they were finished or not (laughs)" (female, translated, 29 years).

> "/…/ the first time I went, was probably the worst as I did not know what to expect, I thought it would be horrible but now, it's kind of like going to the dentist (laughs), I don't hate it that much, it's more of an inconvenience" (female, 35 years).

Only 28.8% (23/80) described it as a painful experience:

> "Sigh…it is really not nice, I experience so much pain during the colonoscopy" (female, translated, 22 years).

> "Every year it is so terribly sore, and then I am also so sick afterwards - at times I am terrified to come, but I do it for the benefit of my health, I just have to" (female, translated, 39 years).

Pain, experienced during the colonoscopy, was cross-tabulated with actual adherence (Table 36). The results show that the observed values are close to the expected values based on the margins and therefore negate a relationship between missed attendance and pain associated with the endoscopic procedure.

Table 36: Cross-tabulation of pain and adherence (n=73).

			Pain group		Total
			Painful	Not painful	
Adherence	Attended all	Count	4	14	18
		Expected Count	5.7	12.3	18.0
	Missed 1	Count	7	20	27
		Expected Count	8.5	18.5	27.0
	Missed 2	Count	5	7	12
		Expected Count	3.8	8.2	12.0
	Missed 3	Count	2	4	6
		Expected Count	1.9	4.1	6.0
	Missed >3	Count	5	5	10
		Expected Count	3.2	6.8	10.0
Total		Count	23	50	73
		Expected Count	23.0	50.0	73.0

The seven participants who had never undergone a colonoscopy were excluded from the analysis.

Pain occurred during the procedure, particularly at the junction of the descending and transverse colon, where the colonoscope has to manoeuvre a near 90 degree angle. Pain was also experienced after the procedure, this was largely due to air trapped in the bowel as a result of the air blown into the colon to aid the visibility during the procedure. For a few participants (4/80), feelings of anxiety were evoked prior to the procedure and related specifically to fears of finding a polyp or a cancer during the colonoscopy:

> I'm always worried, see one does not know what the outcome will be, it's always a relief when you are done and all is okay. But I have made peace with the whole thing, so if the result comes back bad one day I will accept it /…/ sometimes I am just a little queasy before, the nerves you know" (male, translated, 41 years).

Of concern is that a few studies have reported that fear of finding cancer is a barrier to screening (Kruger et al 2005; Natale-Pereira et al 2008; Subramanian et al 2004). The adherence group for these four participants were Group 4 (P7, P47), Group 3 (P48) and Group 2 (P1), which confirms

non-adherence among a group of individuals who experienced anxiety prior to colonoscopies.

The seven participants who had never been for a colonoscopy had heard that it was painful:

> ―I have heard it is very sore, I guess it made me scared and as a result I decided not to go for it" (female, translated, 40 years).

The two participants who indicated ‗other' described the procedure in light of their fear of needles. As the colonoscopic procedure is usually performed under sedation, the sedative is given through an intravenous drip. Although greater levels of sedation lead to less pain and discomfort during the procedure (McCann et al 2009), the trypanophobia could act as a potential barrier to future screening adherence.

Half of the participants (50%) did not view the colonoscopy as a negative experience, which is in line with the results of Jones et al (2009), Pylvänäinen et al (2006) and McCann et al (2009). As found by Liljegren et al (2004), the level of discomfort is also likely to decrease with an increased number of colonoscopies. However, those who did experience pain may demonstrate anxiety about future colonoscopies which could influence their compliance with screening. Furthermore, discussion about the negative experience may affect uptake among relatives, as was the case for some of the seven non-adherent participants, who avoided screening as a result of the relayed description of the procedure.

Encouragingly, 91% of participants (who had a previous colonoscopy) were adamant that they would attend for screening again.

Gynaecological screening

Wagner et al (2005) reported that 69% of their female mutation-positive cohort, over the age of 35 years, underwent gynaecological screening (CA-125 screening and TVU). Of the 55 women involved in this study, 45 were over the age of 35 years. Sixty-two percent (28/45) of these women had been for a ‗regular' gynaecological check-up and 31.1% (14/45) for endometrial cancer screening (endometrial Pap smear and TVU). While these rates are lower than those reported by Wagner et al (2005) screening, in the SA cohort, includes intrauterine biopsy of the endometrium which has been shown to increase detection rates (Renkonen-Sinisalo et al 2007). These low rates are however still of concern as the lifetime risk of developing endometrial cancer in LS has been suggested to exceed the CRC risk for women (Hampel et al 2005b). However, Stupart et al (2009a) has predicted a lower lifetime risk in the SA population (3%), specifically in those with the common founder mutation in MLH1.

Facilitators and barriers to adherence

Participants were asked to identify the reasons for attending their colonoscopic screening appointments. A list of facilitators was discussed with them and they were given the opportunity to highlight any further reasons for non-adherence. The facilitators were identified from the literature, with particular focus on those influencing screening practises in developing communities (Guerra et al 2005; Natale-Pereira et al 2008; Northam et al 2010; Kruger et al 2005)

Table 37 shows the frequency of responses to these selected facilitators and barriers of adherence.

Table 37: Rating frequencies per item on the facilitator and barriers to adherence scale (n=80).

		Items	Main reason -1	Play's a part in going -2	Not a reason -3
			1	**2**	**3**
C9a	Facilitators	Maintain health	70	3	7
C9b		Recent death/affected relative in family	50	14	16
C9c		Other family members go	12	8	60
C9d		Polyp/cancer found previously	28	1	51
C10a	Barriers	Colon preparation	8	3	69
C10b		Discomfort of procedure	2	3	75
C10c		Reported painful experience	2	2	76
C10d		Transport problems	8	0	72
C10e		Do not think that I need it	1	0	79

Figure 27 and 28 display the main factors associated with adherence and non-adherence.

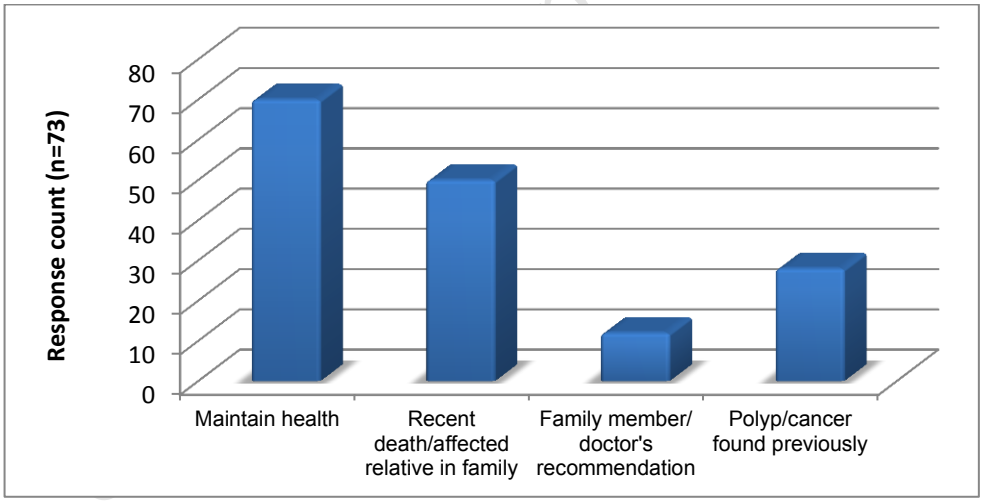

Figure 27: Major facilitators of adherence (items are not mutually exclusive). The seven participants who had never had a colonoscopy were excluded from the analysis on adherence (n=73).

Seventy individuals (97.6%) selected ‗maintaining health' as their primary reason for attendance. Women, especially mother's, highlighted that they were adhering to screening recommendations not only for themselves but for the future of their children:

―You can't be reckless with this thing, so many of my family are and could have been helped if they had only come, I mean you have your children and family to think of…I want to be

around for them, to see them finish school, get married, have children of their own…my mother was not around and I will not do the same to my child, I just have to go…to keep myself healthy and alive for them" (translated, female, 40 years).

The influence of a cancer diagnosis or related death in the family attributed to 68.2% (50/73) of responses. Individuals witnessing suffering in the form of a relative's illness or death often promotes adherence to screening (McCann et al 2009). The influence of the family or healthcare professional on attendance was surprisingly low (12/73). This is in contrast to numerous studies which highlight that the healthcare professional's endorsement of surveillance acts as a major facilitator of CRC screening (Gili et al 2006; Hadley et al 2004; Natale-Pereira et al 2008). The most plausible explanation might be that the participants did not disregard the recommendation from the physician, but rather underwent self-motivating behaviour. Their attendance was a result of seeing the effect of others not going and thereby recognising the benefits for their health. Furthermore, 28 of the 45 affected participants with a previous polyp/cancer (62.72%) selected that the specific pathology had played a major role in their future attendance (Figure 17).

Barriers to adherence

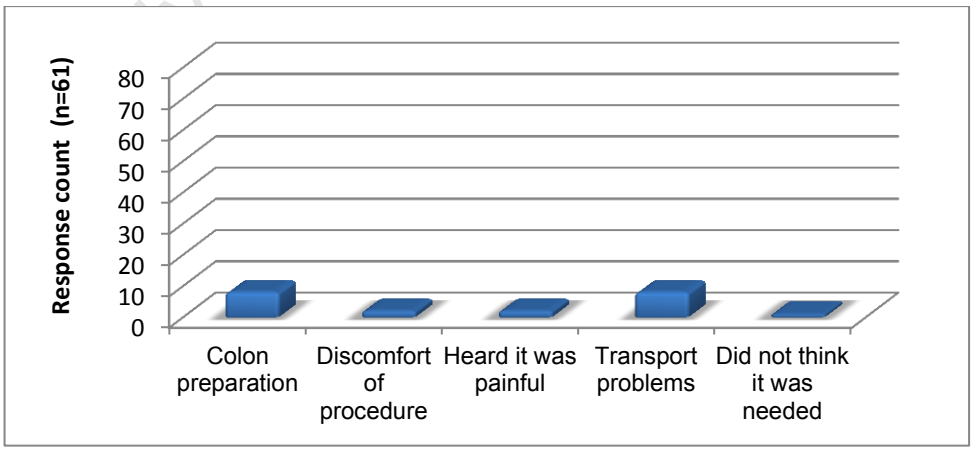

Figure 28: Major barriers to adherence (items are not mutually exclusive). Participants within Group 1 (attending all recommended colonoscopies) have been excluded (n=61).

Figure 28 depicts the main barriers to adherence within the sample group (n=61). Participants who had never missed a colonoscopy were not included in the analysis on non-adherence. The frequencies of each of the categories are low in comparison to those of the facilitators highlighted in Figure 27. Colon preparation (17.1%) and transport problems (17.1%), while representing a low frequency were mentioned most often. It is encouraging to note that while colon preparation rated ‗unpleasant' for 48.8% (39/80) of participants, it reportedly only affected non-adherence to screening for 17.1% of participants.

Additional barriers identified by the participants are presented in Table 38 (items were not mutually exclusive). All-Pay refers to the monthly government-grant pay out. For 11 participants (18.7%) non-adherence was attributed to the fact that the government grant ‗income' had to be collected in person, the date of which co-incided with the surveillance appointment. The majority of these barriers (items 1-8) have not been reported previously and may be specific to the GESC. The perceived barrier (item 9), including the fear that a tumour may be detected during a colonoscopy, or non-compliance as a result of the absence of concerning symptoms, are in accordance with previous observations (Bleiker et al 2005; Stoffel et al 2003). In contrast to the findings of the present study, two smaller SA qualitative studies (n=16 and n=8) found the actual procedure and preparation process to be the main reason for non-adherence (Kruger et al 2005; Northam et al 2010). While these barriers were mentioned by the participants, they only accounted for 20.4% of non-adherence.

Table 38: Additional barriers to adherence (specific to the GESC) (n=61).

Item no.	Response	Frequency	Percentage
1	All-Pay	11	18.7%
2	Pregnancy	8	17.1%
3	Work commitments	8	17.1%
4	Family commitments	6	9.9%
5	Uncertain of date of appointment	5	8.2%
6	Uncertain of frequency of screening	5	8.2%
7	Toilet facilities	4	6.6%
8	Family unaware of result (non-disclosure)	3	4.9%
9	Avoidance		
	• Cancer is inevitable	2	3.3%
	• Ignorance is bliss/concern of finding cancer	3	4.9%
	• Feels healthy (no symptoms)	2	3.3%

Factors affecting adherence to screening

Attendance at either the outreach or hospital sector was not expected to influence compliance as the service offered, operates in exactly the same manner. However, this was investigated to ensure that it was not a contributing factor (Table 39).

Table 39: Adherence to recommended screening guidelines defined by clinic (outreach versus hospital).

			GESC		Total
			Outreach	Hospital	
Adherence	All compliant	Count	14	5	19
		Expected Count	12.4	6.7	19.0
	Missed 1	Count	19	8	27
		Expected Count	17.6	9.5	27.0
	Missed 2	Count	4	8	12
		Expected Count	7.8	4.2	12.0
	Missed 3	Count	5	1	6
		Expected Count	3.9	2.1	6.0
	Missed >3	Count	10	6	16
		Expected Count	10.4	5.6	16.0
Total		Count	52	28	80
		Expected Count	52.0	28.0	80.0

Some cells have too little information to look for statistical differences, in particular those in the hospital sector. By comparing the differences between expected (based on margins) and observed occurrences, the only adherence group which seems to deviate is ‗missed 2' and ‗missed 3'. However, the latter is difficult to interpret due to the single cell observation. Even if adherence groups are reduced to two levels: adherent versus non-adherent,

the difference between adherence to the outreach and the hospital sector is non-existant (Table 40).

Table 40: Adherence to recommended screening guidelines (compliant versus non-compliant) defined by clinic (outreach versus hospital).

			GESC		Total
			Outreach	Hospital	
Adherence	All compliant	Count	14	5	19
		Expected Count	12.4	6.7	19.0
	Non-compliant	Count	38	23	61
		Expected Count	39.7	21.4	61.0
Total		Count	52	28	80
		Expected Count	52.0	28.0	80.0

Educated individuals are suggested to be more knowledgeable on the benefits of screening for CRC and likely to be more compliant than those with lower education backgrounds (Subramanian et al 2004). The relationship between a higher education and greater adherence did not explain compliance in this study (Table 41).

Table 41: Cross-tabulation of education with adherence group (n=80).

Education		Adherence					Total
		All compliant	Missed 1	Missed 2	Missed 3	Missed >3	
	≤ Senior schooling	16	24	10	6	13	69
		(27.2%)	(31.8%)	(14.2%)	(8.7%)	(18.7%)	(100%)
	≥ College/university	3	3	2	0	3	11
		(27.3%)	(27.3%)	(18.2%)	(0%)	(27.3%)	(100%)
Total		19	27	12	6	16	80
		23.8%	33.8%	15%	7.5%	20%	100%

Some percentages may not add up to a 100% as a result of rounding-off.

Previous studies examining screening practices have found that gender can affect adherence (Codori et al 2001; Denberg et al 2005; Gili et al 2006; Weitzman et al 2001). With regard to this study, no relationship was found between gender and the adherence[4] of the participants (Table 42).

[4] To test the relationship, the three last categories were considered as one category to obtain sufficient observations per cell.

Table 42: Cross-tabulation of gender and adherence (n=80).

	Adherence					Total
	All compliant	Missed 1	Missed 2	Missed 3	Missed> 3	
Male	7	9	5	1	3	25
	(28%)	(36%)	(20%)	(4%)	(12%)	(100%)
Female	12	18	7	5	13	55
	(21.8%)	(32.7%)	(12.7%)	(9.1%)	(23.6%)	(100%)
Total	19	27	12	6	16	80
	(23.8%)	(33.8%)	(15%)	(7.5%)	(20%)	(100%)

Nor did the gender of the parent (with LS) of the participant affect adherence. Table 43 shows the relationship between actual adherence of the participant per gender of the affected and unaffected parents.

Table 43: Participant adherence cross-tabulated with gender of affected and unaffected parent (n=80).

		Adherence					Total
		All compliant	Missed 1	Missed 2	Missed 3	Missed >3	
Affected	Male	11	13	6	1	5	36
	Female	7	12	6	4	8	37
Not Affected	Male	0	2	0	0	0	2
	Female	0	0	0	1	2	3
	Unknown	1	0	0	0	1	2
Total		19	27	12	6	16	80

Likewise the relationship between the type of referral and adherence did not account for non-adherence (Table 44).

Table 44: Cross-tabulation of adherence and referral type (n=80).

Referral	Adherence					Total
	All compliant	Missed 1	Missed 2	Missed 3	Missed >3	
Clinic	3	4	1	1	1	10
Self	0	1	1	1	0	3
Family	9	9	6	3	9	36
Recruited by GESC	7	12	3	1	5	28
Total	19	26	11	6	15	77

A relationship between age and non-adherence seems to exist. The youngest age group had the least ‗missings' (over-represented within the adherent groups) whereas the group in the age 40 to 49 show the most ‗missings' (over-represented in the group with a higher absence rate) (Table 45). The results suggest that underlying factors related to age could explain the absence to screening practices following the delivery of a mutation-positive result (Crochbach alpha = 0.83). Previous reports have highlighted similar findings in individuals with a family history of CRC (Denberg et al 2005; Gili et al 2006; Glanz et al 1999).

Table 45: Adherence per age group (n=80).

		Adherence					Total
		All compliant	Miss1	Miss2	Miss3	Miss>3	
Age	20-29	5	2	1	0	2	10
	30-39	6	9	5	2	2	24
	40-49	5	10	2	2	9	28
	≥ 50	3	6	4	2	3	18
Total		19	27	12	6	16	80

The number of missed colonoscopies for each participant within the four specified age groups is illustrated graphically in Figure 29.

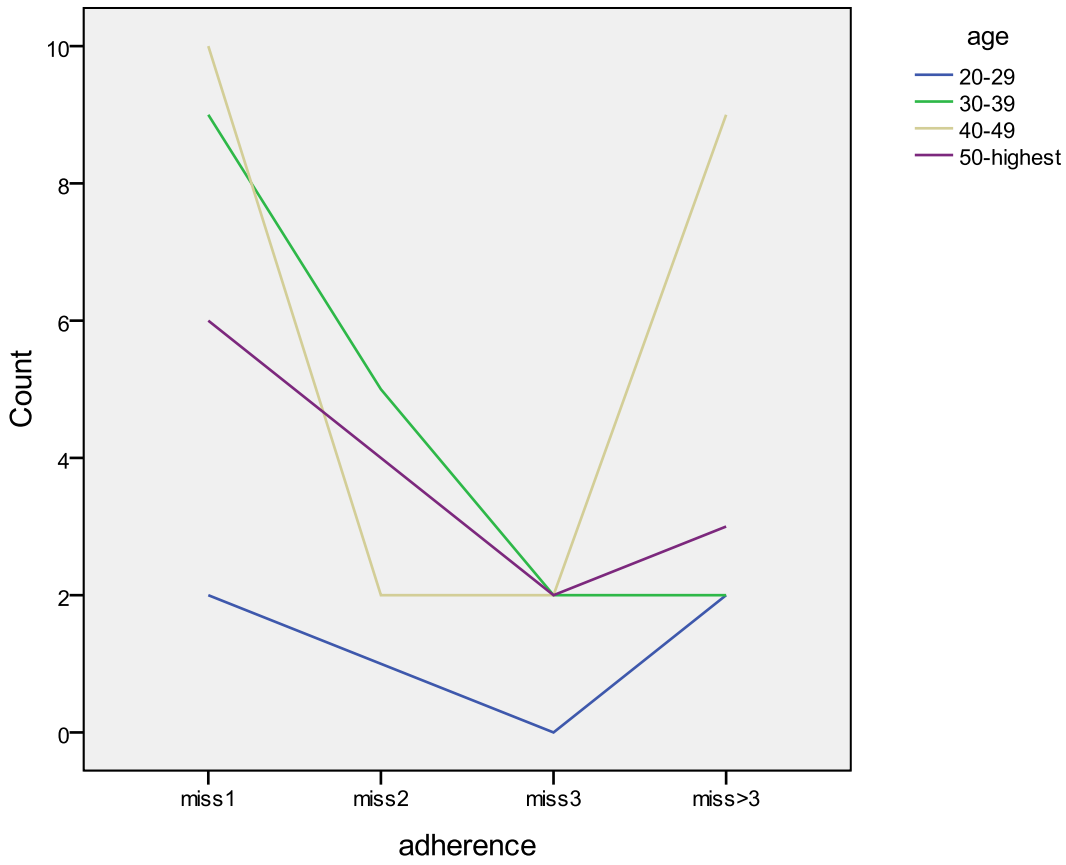

Figure 29: Adherence per age group (n=80).

Possible explanations for this could be that uptake could be easier to maintain if recommendations are every two years instead of annually (≤ 30 years of age according to screening guidelines in SA). Being younger and more proactive about health could also enhance greater adherence among this group of individuals.

Table 46 suggests that knowing a family member with cancer does not necessarily increase actual adherence. For 55 participants (68.8%), the effect of a parent/family member‘s cancer diagnosis had led them to become more adherent, however these participants were mostly from compliant groups: Group 1 (attended all colonoscopies) and Group 2 (missed one colonoscopy). For 18 participants no resultant effect on adherence occurred and no participants reported that the parent/family member‘s cancer had caused them to become less adherent.

Table 46: Attitude to surveillance following a family member's cancer cross-tabulated with actual adherence (n=80).

	Adherence					Total
	All compliant	Missed 1	Missed 2	Missed 3	Missed >3	
More adherent	13 (16.3%)	21 (26.3%)	9 (11.3%)	4 (5%)	8 (10%)	55 (68.8%)
No change to adherence	4 (5%)	4 (5%)	3 (3.8%)	2 (2.5%)	5 (6.25%)	18 (22.5%)
Not applicable	2 (2.5%)	2 (2.5%)	0 0%	0 0%	3 (3.8%)	7 (8.8%)
Total	19 (23.8%)	27 (33.8%)	12 (15%)	6 (7.5%)	16 (20%)	80 (100%)

Not applicable' applies to individuals who were not exposed to a family member's cancer.
Some percentages may not add up to a 100% as a result of rounding-off.

Furthermore, acting as a care-giver for an affected family member did not influence adherence rates. The results of Table 47 show that the observed values are close to the expected values based on the margins.

Table 47: The relationship between adherence and the level of care involvement.

			Care-giver		Total
			Yes	No	
Adherence	All compliant	Count	5	14	19
		Expected Count	6.4	12.6	19.0
	Missed 1	Count	10	17	27
		Expected Count	9.1	17.9	27.0
	Missed 2	Count	3	9	12
		Expected Count	4.1	8.0	12.0
	Missed 3	Count	3	3	6
		Expected Count	2.0	4.0	6.0
	Missed >3	Count	6	10	16
		Expected Count	5.4	10.6	16.0
Total		Count	27	53	80
		Expected Count	27.0	53.0	80.0

A common barrier to surveillance is lack of any or adequate health insurance (Natale-Pereira et al 2008) or the concern about losing health insurance coverage or increased tariffs (Lynch et al 1993a). In SA, and particularly at the outreach GESC these factors are unimportant as screening is offered free of charge. Furthermore, no participants reported that insurance concerns played a role in delaying screening.

Many of the recognised barriers and facilitators to screening practices have been derived from studies looking at CRC families without a known genetic mutation (Codori et al 2001; Beeker et al 2000; Gili et al 2006; Guerra et al 2005; Harris et al 1997; Natale-Pereira et al 2008; McCarthy et al 1993; Weitzman et al 2001). This suggests that these findings may not be generalised to families with LS attending the GESC, even though they share a common cancer basis.

Understanding of colonoscopic results

The understanding of the outcome of the colonoscopy is presented in Table 48. The majority of participants received feedback following their colonoscopic screening and illustrated a clear understanding of the outcome of their procedure. The purpose of the colonoscopy was described with varying degrees of insight: _aprocedure which can see if you are healthy', _a procedure that can look at the inside of the colon', _aprocedure which can identify cancer early', _a procedure which can identify growths in your colon which can develop into cancer if not removed', _aprocedure which is able to get a good view of your colon and also able to take biopsies'. A few participants knew that a polyp had the potential to develop into a malignancy:

> /../ they need to check it out with a biopsy as the polyp is a precursor to cancer" (male, 43 years).

> It can just be that if you miss one year, that that growth starts developing and you have not seen it because you missed the test [colonoscopy], so if you stay away for say three years, then it is a problem, you could be looking at a far worse picture and it would really just be your own fault if you ended up in that position" (translated, female, 58 years).

Other participants described it as a _growth', a _wart', a _sore' or a _dot/mark' on the colon. While they knew that it required removal they made no mention of the concern for cancer development. Mostly, participants had not heard the term before or could not explain what it meant if a polyp was identified during a colonoscopy. This finding is of concern, as the benefit of

polypectomies, which can substantially reduce the risk of CRC, may not be fully understood (Liljegren et al 2004).

Knowing when the next colonoscopy would occur and being in possession of the GESC contact details rated highly among the participants (Table 48). However, when appointments were missed, they were only rescheduled in a minority of cases. For the participants attending the outreach GESC, the reasons for not rescheduling were attributed to rather waiting another year to be seen by the GESC staff than by different doctors (without previous management experience within their family).

Table 48: The occurrence of categories of a subset of variables relating to colonoscopic screening.

Item	Description	Frequency	Percentage
C11	Colonoscopic results given following procedure	69/73*	94.5%
C12a	Results understood by participants	66/73*	90.4%
C13a	Future date for colonoscopy known	72/80**	90%
C14	In possession of a contact number for the clinic	66/80**	82.5%
C15	Missed appointments rescheduled	13/61***	16.3%

*Total count (73) reflects the number of participants who have had one or more screening procedures.
**Total count (80) reflects that this question was applicable to all the participants.
***Total count (61) is a reflection of the number of participants who have missed a screening procedure and excludes the 19 participants who have attended all their scheduled colonoscopies.

4.6 SATISFACTION WITH THE GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC (GESC)

Table 49: The rating frequencies per item on the GESC satisfaction scale (n=80).

	Items	Yes	No
D1a	**Everyday language was used to explain LS** (Home language was used, easy to understand concepts used to explain)	74 (92.5%)	6 (7.5%)
D1b	**Everything I wanted to know about LS was explained at the clinic** (Cause, age of onset, symptoms, reason for surveillance)	78 (97.5%)	2 (2.5%)
D1c	**The counselling received helped me cope better with my condition/risk of developing the condition**	74 (92.5%)	6 (7.5%)
D1d	**I will follow the clinics advice because I think they are absolutely right** (Come for a colonoscopy every year/gynae visits etc/talk to family about risk)	79 (98.1%)	1 (1.3%)
D1e	**I understand why my family has a higher risk than other families of developing cancer** (What were you told was the reason for the high-risk)	52 (65%)	28 (35%)
D1f	**The time I spent at the clinic was long enough to deal with everything I wanted to discuss** (How much time did you spend with the staff, did you feel this was long enough)	74 (92.5%)	6 (7.5%)
D1g	**The Dr/nurse/counsellor was easy to reach after the clinic consultation for any questions/concerns that I had** (Were they contacted, was there a need to contact)	79 (98.1%)	1 (1.3%)
D1h	**Were any of your questions unanswered?** (Did you have any questions at visit, after visit, were they answered)	12 (15%)	68 (85%)

LS-Lynch syndrome.

Table 49 shows that most patients were satisfied with their GESC consultation when measured by the eight dichotomous statements. Although most items in Table 49 showed little variance, a homogeneity analysis using CAT-PCA, that treated the variables as single nominal, was conducted. The accompanying component loadings are presented in Table 50.

Table 50: Component loadings per item of a two dimensional CAT-PCA on the GESC satisfaction scale (n=80).

Items		Dimensions	
		1	**2**
D1a	Everyday language was used to explain LS (Home language was used, easy to understand concepts used to explain)	0.668	-0.131
D1b	Everything I wanted to know about LS was explained at the clinic (Cause, age of onset, symptoms, reason for surveillance)	0.635	-0.319
D1c	The counselling received helped me cope better with my condition/risk of developing the condition	0.679	0.050
D1d	I will follow the clinics advice because I think they are absolutely right (Come for a colonoscopy every year/gynae visits etc/talk to family about risk)	n/a*	n/a*
D1e	I understand why my family has a higher risk than other families of developing cancer (What were you told was the reason for the high-risk)	0.130	0.839
D1f	The time I spent at the clinic was long enough to deal with everything I wanted to discuss (How much time did you spend with the staff, did you feel this was long enough)	0.636	-0.118
D1g	The Dr/nurse/counsellor was easy to reach after the clinic consultation for any questions/concerns that I had (Were they contacted, was there a need to contact)	n/a*	n/a *
D1h	Were any of your questions unanswered? (Did you have any questions at visit, after visit, were they answered)	-0.379	-0.587

*Items D1d and D1g were not included in the analysis as the responses failed to generate sufficient variance.
LS-Lynch syndrome.

The component loadings are presented as vectors in two-dimensional space (Figure 30). This aids the identification of a possible clustering of items. Item D1g and D1d were excluded from further analysis as only a single patient claimed that she would not follow the ‗clinics advice' and that she had difficulty contacting a ‗healthcare professional'. The participant was a 50 year old female who had missed one of her recommended colonoscopies and also rated items D1c-D1g as unsatisfactory. This participant's score for the satisfaction with the GESC is presented in Table 51.

Table 51: Rating per item on the GESC satisfaction scale for P59.

	D1a	D1b	D1c	D1d	D1e	D1f	D1g	D1h
P59	1	1	2	2	2	2	2	2

1= yes, 2= no to items on GESC satisfaction scale.

The co-ordinates of the vectors of the variables in the plot are the components of each variable per dimension. Figure 30 reveals two sets of clusters. This suggests that these questions address different aspects of satisfaction. For example, items D1e and D1h, are related and strongly dominate dimension 2 (longest vector) although the items are projected opposite each other. The clustering can be seen when considering the mirror image of D1h. D1e refers to ‗struggling with understanding why the family is at a higher risk' and D1h ‗questions unanswered following consultations'.

The next cluster is formed by items D1a, D1b, D1c and D1f. These items dominate the first dimension. The length of these vectors are almost equal and in the same direction suggesting that these items are more or less equal in their weight to define the first dimension. However, the close proximity of items D1f to D1b indicates that the individual's perception of ‗length of time of the appointment' is strongly associated with ‗having all information on LS explained'. The close projection to items D1c and D1a suggests that having ‗information explained in a home language' and ‗counselling that leads to coping with the risk of developing LS' lead to greater satisfaction.

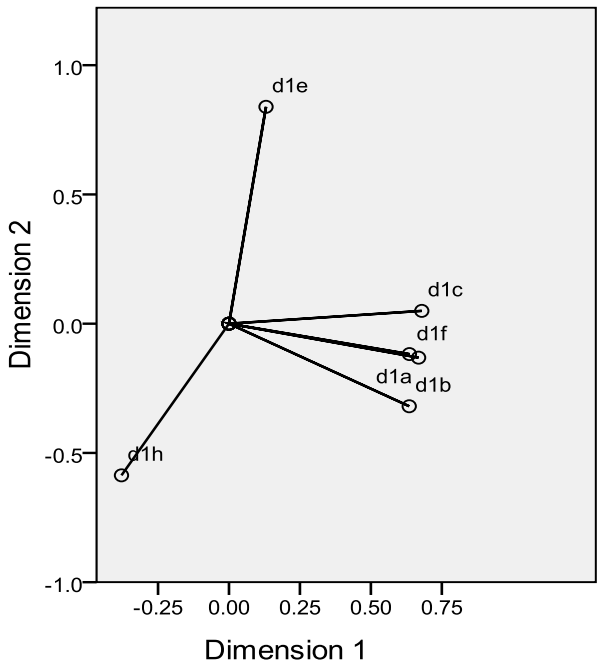

Figure 30: A plot of the component loadings of the six items on the GESC satisfaction scale.

The second figure shows how the categories are related (Figure 31). The plot of the category points suggests a relationship. On the second dimension, category two of D1e is projected relatively close to category one of D1h (top left quadrant). Thus ‗struggling with understanding why one's family is at higher risk' is related to participants having ‗questions unanswered'. Whereas, category one of D1e is close to category two of D1h (bottom left quadrant). Thus ‗understanding why one's family is at higher risk' is related to ‗questions were answered'.

The categories belonging to items D1a, D1b, D1c, and D1f are clearly separated with the ‗ones' on the left side of the origin (0, 0) and the ‗twos' on the right side of the origin. Category two of Item D1b is at a distance and the two patients that said ‗no' to item D1b behave as outliers.

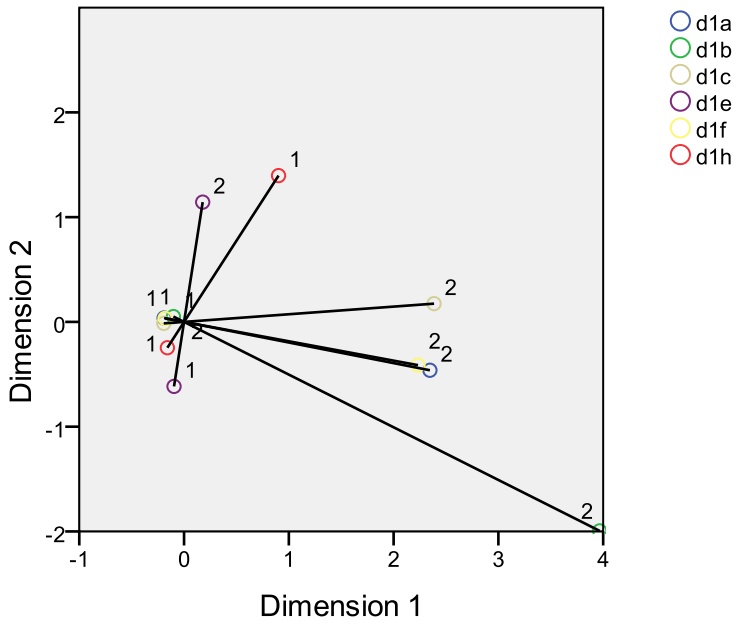

Figure 31: Plot of category points of the six items on the GESC satisfaction scale.

Further analysis revealed tendencies of gender differences. Those that ‗struggle with understanding why their family is at risk' and ‗have questions unanswered' appear to be predominantly males. Whereas those who claim to

‗understand the higher risk' and ‗have questions answered', appear predominantly female. This is apparent in Table 52. More males than expected struggled with understanding whereas more females than expected claimed to understand the higher risk.

Table 52: Understanding of familial risk per gender of participants (n=80).

D1e - ‗understanding of familial risk'				
		Understands	Does not understand	Total
Male	Count	15	10	25
	Expected Count	16.3	8.8	25.0
Female	Count	37	18	55
	Expected Count	35.8	19.3	55.0
Total	Count	52	28	80
	Expected Count	52.0	28.0	80.0

More males than expected had questions unanswered whereas more females than expected had no questions unanswered (Table 53).

Table 53: Questions addressed at GESC per gender of participants (n=80).

D1h - ‗questions addressed'				
		Questions unanswered	Questions answered	Total
Male	Count	5	20	25
	Expected Count	3.8	21.3	25.0
Female	Count	7	48	55
	Expected Count	8.3	46.8	55.0
Total	Count	12	68	80
	Expected Count	12.0	68.0	80.0

In both tables above, however, numbers were too small to reach statistical significance.

Furthermore, knowledge about LS did not relate to lack of understanding or questions unanswered (Table 54).

Table 54: Cross-tabulation of knowledge with understanding of a familial risk (n=80).

			Understanding of familial risk (D1e)		Total
			1 - yes	2 - no	
Questions addressed	Knowledge	<50%	1	0	1
		50%	0	1	1
		60%	2	1	3
		75%	2	4	6
		>75%	0	1	1
	Total		5	7	12
Questions not addressed	Knowledge	<50%	10	7	17
		50%	11	5	16
		60%	11	6	17
		75%	11	3	14
		>75%	4	0	4
	Total		47	21	68

Knowledge is expressed as a percentage of correct answers to knowledge questionnaire (Domanska et al 2009).

An indicator, however, of the success of the recruitment program is that those who were recruited by the GESC show better performance in ‗knowledge' with only just over ten percent scoring less than 50% (Table 55).

Table 55: Knowledge cross-tabulated with referral type (n=80).

Referral	Knowledge					Total
	<50%	50%	60%	75%	>75%	
Local clinic	3	2	2	3	0	10
Self	1	1	0	1	0	3
Family	11	6	7	9	3	36
Recruited by GESC	3	6	11	6	2	28
Total	18	15	20	19	5	77

Although the large majority of participants were satisfied with the service offered by the GESC, several areas amenable to improvement were identified by the participants and are discussed under recommendations in Section 6.1.

4.7 COMMUNICATION WITHIN THE FAMILY

The varying emotional reactions, among the 80 participants, to being informed about a positive PT are presented in Table 56. Quotes have been included to support the classification of a particular code for the given responses.

Table 56: Emotional reaction to receiving a mutation-positive test result.

Emotional response to receiving a mutation-positive test result	Frequency of responses (_/80)	Quotes used to exemplify particular response category
Shock/disbelief	15	—I thought…I can't even share this with my husband, I let him believe all was fine. I was so scared I could not handle it, I don't know why, but it was such a shock…that day I was feeling fantastic, felt so good, did not think for one moment that the result would mess up my life like it did. [Genetic counsellor] asked me how I felt before she gave the result and I said I felt quite fine I have had three months to think about it and prepare myself for the result...but it was a real shock" (translated, female, 37 years). —Initially, it was a huge shock, I did not even discuss it with my family, I told [genetic counsellor] that she cannot tell anyone about the result, I begged her and I walked out of the clinic like nothing had happened - I smiled - everyone asked about the result but I said that I was ok, they believed me /…/" (translated, female, 43 years).
Expectation as a result of:	14	
Symptoms/prior cancer diagnosis		—The counsellor had this long and in-depth discussion, my sister and I went together and she was almost overly sensitive and understanding and we were rather blasé because at the time I had already developed a bad polyp so I was not really expecting that I would not have it [gene]. It was not really anything that made me emotional - I did not hold out any hope that I would not have it - you know my gran had it, my mom had it and I had it" (female, 35 years). —I knew I would be positive, because I had already had cancer, so it was not a shock to find out that I had the gene" (female, 47 years old).
Multitude of family members/hereditary		—I was not surprised that I had the gene, my father died of cancer, his brother and his sister has cancer, my father's mother also died of cancer. It actually made it easier because now I know the reason for what happened to them" (translated, male, 42 years old). —I was expecting it, you see I know this problem is in my family- it was not really a shock to hear" (translated, female, 33 years old).
Similar personal characteristics/ resemblance		—I expected to have it, you see I am very close to my father, very similar to him in so many ways, so if anyone was going to have it, it was going to be me" (translated, female, 24 years old).

Table 56: Emotional reaction to receiving a mutation-positive test result (continued).

Emotional response to receiving a mutation-positive test result	Frequency of responses (_/80)	Quotes used to exemplify particular response category
Practical/logical	8	"I know it means that I may require an operation one day, but it is good to know as I can plan around this thing" (translated, male, 40 years). "/…/ look, it was good to find out about it and the result did not necessarily mean that we would get cancer, it's just a possibility - it was actually a very good thing to hear" (translated, male, 40 years). "I was terribly nervous, you think the worst, but [genetic counsellor] explained it so nicely that I, I understood and it was easy to get over it - you realise you have the gene, you are a carrier but you don't think of it as this terrible thing anymore. Once someone tells you what it is all about, then it is actually easier to accept /…/" (translated, female, 44 years).
Acceptance/reasoning	7	"I guess I felt alright, I could not do much about being positive. I could not go getting down about the whole thing. You see, there is a reason why I am positive, when my sister was in the hospital, when she got it, she was very upset, she could not understand why she got cancer and no one else, I was older than her, why did I not also have it, but when she found that I also had it, that I was positive, its almost as if we could make it through this thing if we were together in it - now both of us at least have the same thing and she can deal with her cancer" (translated, female, 49 years).
Hard/difficult to hear	6	"When I walked to the hospital to get my results I had a feeling that it may well be positive, but when I heard it…it was difficult, it was very difficult" (translated, female, 50 years).
Anxious	4	"I was very nervous that day, I did not expect to hear that I had the gene - maybe I could be one of the lucky ones…but I felt more relaxed once I heard all the information, I was still worried though /…/" (translated, female, 44 years).
Cancer diagnosis	4	"See I thought that high-risk meant you would get sick that you were told you sort of had a cancer, so it was a shock, at a later stage [genetic counsellor] explained some things to me again and I could appreciate what high-risk meant, see at that stage I thought I had it" (translated, male, 42 years). "Actually at that stage I thought I had cancer, I was under the impression that…that I had cancer, because they spoke in English and I thought they were telling me the result showed cancer…I thought I had cancer" (translated, female, 27 years).
Sense of unfairness	4	"/…/ why do I have it and not any of my sisters?" (translated, female, 38 years). "/…/ why did I end up with all my father's ailments?" (translated, female, 30 years).

Ten participants could not recall their result disclosure session and response categories could not be determined for these individuals.

Reactions and emotions to a mutation-positive test result

Fifteen participants (18.8%) experienced reactions of shock or disbelief, when receiving a mutation-positive test result. Secrecy around the participant's status often occurred when a negative result was expected, but replaced by a positive one (Table 56). In contrast to this reaction, was the one of an expectation of a positive test result, as occurred in 14 participants (17.5%). According to McAllister (2002) individuals who engage with their cancer-related risk, often believing themselves to be mutation-positive prior to testing, cope well even if the outcome of the result is unfavourable. The benefits of a previous engagement (with the cancer-related risk), were also recognised by Esplen and colleagues, who found that individuals who anticipate having a mutation-positive result experience less distress when receiving positive test results, as they are already engaging in an active coping strategy (Esplen et al 2007). The findings from this study suggests that expectation occurs as a result of a previous cancer diagnosis (Esplen et al 2007), the presence of existing symptoms, a multitude of family members with CRC or the recognition of an inherited familial risk and the resemblance to a mutation-positive family member (McAllister 2002; McAllsiter 2003).

Participants receiving the news in a positive light were either practical (8/80) or illustrated an acceptance or reason (7/80) for the mutation-positive result. Several participants expressed this view as a result of a process of intellectualisation listing the benefits of surgery, screening and incomplete penetrance. They recognised the benefits of knowing about their CRC-related risk. The news was difficult to hear for six participants, anxiety-provoking for four and associated with a sense of unfairness for 5% (4/80). Of concern, were the 5% of participants (4/80) who misconstrued their result interpreting it as a definite cancer diagnosis instead of a cancer-related lifetime risk.

Disclosure of mutation-positive test results

Participants were asked to name the person from whom they obtained the most emotional support subsequent to receiving a mutation-positive result.

Table 57 outlines the individuals involved and illustrates that the majority (62.5%) of participants obtained support from a family member (usually a sibling or parent). This is consistent with the findings of White and Riedmann (1992) and Hughes et al (2002), who confirm that siblings are an important source of emotional support among mutation-positive individuals in HBOC families.

Table 57: Participants' source of emotional support subsequent to receiving a mutation-positive test result.

Support person	Frequency (n=80)	Percentage
Professional	3	3.75%
Family member	50	62.5%
Friend	1	1.25%
Did not tell anyone about genetic test result/did not seek support	24	30%
Member of church	1	1.25%
Other	1	1.25%

Sixty-one participants (76.3%) disclosed their genetic test result the same day. Generally, disclosure to close relatives occurs within 48 hours to a week in LS families (Gaff et al 2005; Hughes et al 2002; Petersen et al 2003). The benefit of timely disclosure is highlighted by Petersen et al (2003) who found that higher uptake rates, of PT in at-risk family members, are seen if there is no delay in disclosure, while lower rates occur when there is a delay. Reasons for disclosure included the fact that the information was not viewed as secret and that it was a family condition:

> "We are not secretive about it - we talk about it, if anyone has ever asked me about it, I have responded very openly /…/ it is nothing to hide or be ashamed of" (translated, female, 46 years).

> "It is not this big scary thing in our lives, so no reason to keep it a secret" (female, 53 years).

Disclosure also occurred when the participant was emotionally close to a particular person, aware that they could trust/confide in or seek support from them. This is clear when considering the responses of P60 and P66:

> ―told her because we are friends and we share everything" (translated, female, 22 years).
>
> ―They must know, they are family…you can't keep this type of thing from them - they are the ones who will be supporting you through it all" (translated, female, 29 years).

Likewise, the information was divulged when trying to engage a particular family member to enter into PT:

> ―told my daughter as soon as I found out about my result, you see she must also be tested…it is better to know to be able to keep yourself healthy /…/ for my son it was too late, my daughter must go, so that they can look after her" (translated, female, 52 years).

The individuals to whom the participants disclosed their PT results and the respective frequencies at which this occurred are presented in Figure 32.

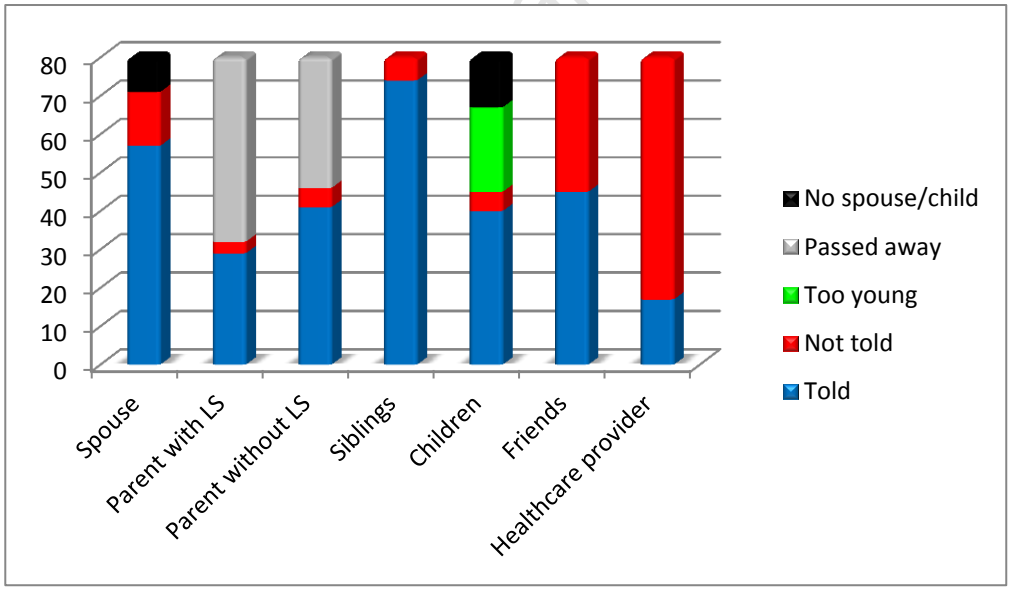

Figure 32: Individuals to whom the participants disclosed their PT results.

Individuals, most often informed about the participant's status, included siblings (74/80), spouses (57/80) and parents. Ninety percent of participants with a living parent with LS reported that they had disclosed their test result to them (29/32). The parent without the family history of LS was informed in 89% of cases (41/46). The high rate of disclosure, among these individuals, are

congruent with other studies (Bonadona et al 2002; Hughes et al 2002; Patenaude et al 2006).

Children were informed about the participants' test result in 45 cases (56.3%). These findings are much lower than those noted by others, who reported a range of 75-90% (Aktan-Collan et al 2011; Ersig et al 2009; Hughes et al 2002; Patenaude et al 2006; Stoffel et al 2008) in LS families but similar to that of disclosure rates in HBOC families (Bonadona et al 2002). Many participants were however waiting until their children were older before informing them.

Discussion was not necessarily limited to persons at-risk of LS. Disclosure occurred to ten work colleagues (12.5%), five participants informed their religious leader (6.25%), and six their employer (7.5%). The employers were informed to explain the two-day request for absenteeism, as is often required, for the preparation and procedure. Of concern, is that only 21.3% (17/80) of participants had informed their general healthcare provider.

Communication about the availability of PT to family members

While disclosure of personal results may have been high among this group (76.3%), 48 participants did not directly discuss the implications of their test result with all their at-risk family members. The majority of participants had also taken several years to inform these individuals about the relevance and importance of finding an inherited predisposition within the family (Table 58). This is in contrast to the timely disclosure of PT results, albeit mostly to FDR, which occurred within 24 hours for more than 50% of the participants. Simply sharing genetic results may not be sufficient to engage relatives with PT, as the availability and benefit for the family member is not always discussed when results are made known.

Table 58: Informing family about risk implications after receiving a mutation-positive test result.

Information related to discussion	Frequency	Percentage
Informed at risk family member of increased risk of CRC		
Yes	32/80	40%
No	48/80	60%
Reason for informing family member		
New recruit for PT	8/32	25%
Non-adherent to surveillance	11/32	34.4%
Never returned for PT result	1/32	3.1%
Average time to informing family member about mutation-positive status		
Immediately after receiving mutation-positive result	8/80	10%
Months after mutation-positive result	4/80	5%
Years after mutation-positive result	11/80	13.8%
Continuously trying to contact family member	6/80	7.5%
Contacts when clinic team requests it	3/80	3.8%
Disclosure of personal test result when informing family of risk		
Yes	29/32	90.6%
No	3/32	9.4%

PT - Predictive genetic testing.

The participants cited various reasons for withholding the information from certain family members. These are presented in Figure 33.

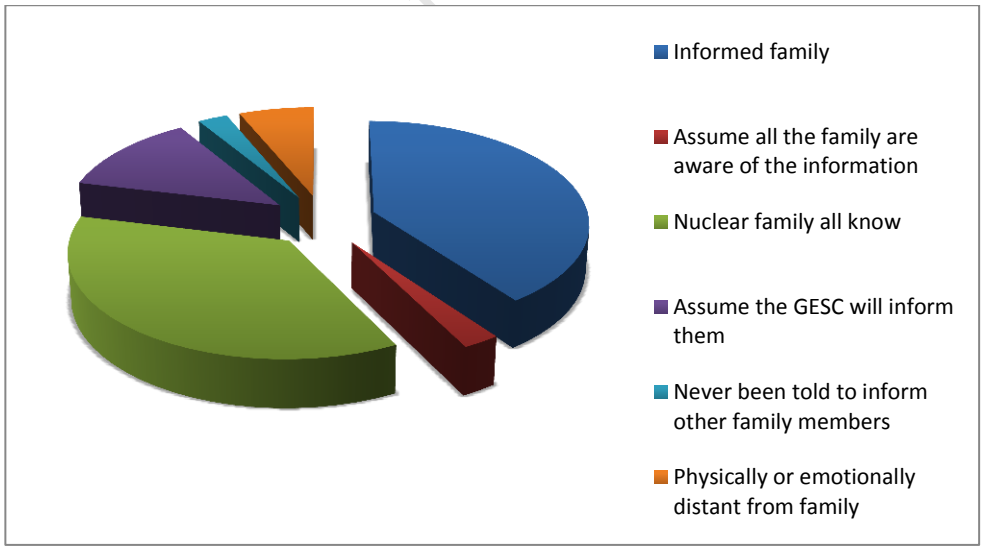

Figure 33: Communication of risk implications (subsequent to receiving mutation-positive test result) within the family.

Informing at-risk family members has been recognised as a burdensome responsibility among more than a third of patients, requesting genetic testing for a cancer susceptibility, following the disclosure of their mutation-positive

test result (Bonadona et al 2002). Sixty percent of participants indicated that there were at-risk family members whom they had not directly informed (Table 58). As is often noted, a conscious decision to withhold information does not necessarily take place (Gaff et al 2005; Peterson et al 2003) and 36.3% of participants limited the disclosure of information to the boundary of their nuclear family, as they felt that it was the responsibility of the parents of cousins to inform second-degree relatives. This is similar to other research findings, which recognise the tendency to restrict information to FDR (Gaff et al 2005; Mesters et al 2005; Petersen et al 2003). Twelve percent of individuals failed to communicate because they viewed it as the role of the GESC, or had never been informed by the GESC to enlighten additional family members (2.5%). Six percent of participants did not pass on information to at-risk relatives as a result of a physical or emotional barrier. This obstacle to disclosure has been documented in multiple cancer-related (LS and HBOC) studies (Claes et al 2003; Gaff et al 2005; Hughes et al 2002; Julian-Reynier et al 2000; McCann et al 2009).

The barriers to communication that were not mentioned, but often occur in cancer families include: making sense of personal risk before consultation with family members about their risk (Keenan et al 2005), having information rejected (Blandy et al 2003; Gaff et al 2005), difficulty in understanding genetic results (Wagner Costalas et al 2003), harmful nature of information (Bonadona et al 2002; d'Agincourt-Canning et al 2001) inappropriate time to disclose (Forrest et al 2003) and being mutation-negative (Foster et al 2004).

It is increasingly recognised that women take on the responsibility for their family's health (Richards et al 1996; Wilson et al 2004) and in the context of communicating genetic risk, women usually take on the responsibility of informing family members about genetic risk in LS and HBOC families (Forrest et al 2003; Koehly et al 2003). The reluctance to inform relatives occurred more frequently among men than women (33.3% versus 19.6%) and confirms the previous reports.

Patients with cancer are also documented key messengers in the discussion of genetic risk within the family (Julian-Reynier et al 2000). Half of the participants with cancer (8/16) told their at-risk family members about the implications of their test result, the other eight participants expressed that all the at-risk family members were already aware of the information. These 16 participants were also more open to disclosing their personal test result with their family. With the exception of one participant who did not disclose his genetic test result to the living parent with the family history of LS, and two participants who did not inform their children (who were under the age of 18 years), disclosure rates were 100% among parents, siblings and children of affected individuals.

Informing children about their inherited risk

Sixty-eight participants had biological children at a 50% risk of inheriting LS. Forty-three of these participants (63%) had informed their children of the inherited nature of the familial cancer. Figure 34 shows the age when the risk/PT had been discussed with the participant's offspring. Information was most often transmitted when the children were between the ages of 17 and 18 years of age (17/43).

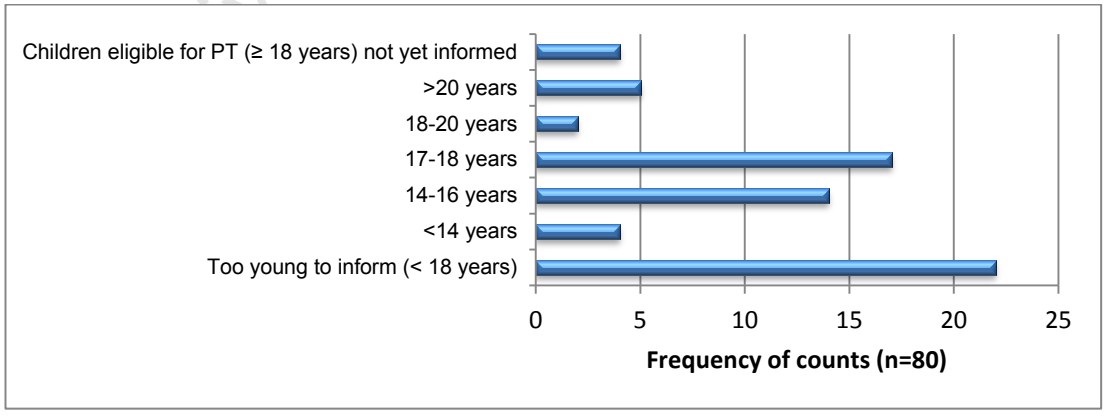

Figure 34: Discussion of PT or cancer-related risk with children.

According to parents, the right time to inform children about an inherited risk is often around key life decisions such as entry into a serious

relationship/marriage or consideration of parenthood (Bonadona et al 2002). Timing of disclosure has also been recognised to occur around the age that the child becomes eligible for cancer surveillance or is considered to be emotionally ready (Aktan-Collan et al 2011; Forrest et al 2003; Mesters et al 2005; Stoffel et al 2008). Similarly, 48.8% of participants in this study discussed PT when their children were old enough to enter into the testing programme or illustrated a mature ability to cope with the information. For 27.9% (12/43) the discussion occurred following a parent's/family member's cancer diagnosis/death, 11.6% (5/43) when children started asking questions about a parent's colon preparation/surveillance appointment and 9.3% (4/43) described that they had always been open about the particular information of being at-risk from when their children were a very young age.

Eighty-eight percent of participants (38/43) mentioned genetic testing (blood test) during the discussion with their children and 83.7% (36/43) informed their children about surveillance. Seventy-three percent (58/80) of participants agreed that PT should be offered at 18 years of age, while 25% (20/80) contested this and suggested an earlier age could be considered. Surprisingly, two (2.5%) participants preferred this to occur at a later stage after 18 years of age.

Discussion of Lynch syndrome-related topics within the family

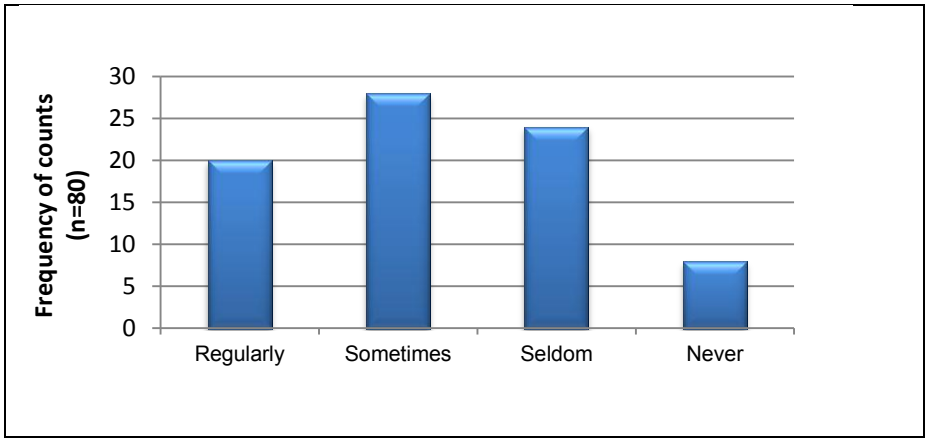

Figure 35: Frequency of discussion of Lynch syndrome-related topics (n=80).

Figure 35 shows that the majority of participants discussed LS-related topics on an infrequent basis (75%). Fifty-three percent (42/80) of participants felt that they had received all the information that they wanted to know about LS; but areas where more information was sought included: ‗origins of family cancer', ‗cause of cancer' and ‗polyp development'.

The greatest need, as expressed by the participants, was for a pamphlet/booklet with information on LS (Figure 36). Currently a pamphlet is available on the preparation process for the colonoscopy, but information on LS is limited to that verbally discussed by the healthcare professional during the session. Participants who cited ‗other' requested information aids in Afrikaans.

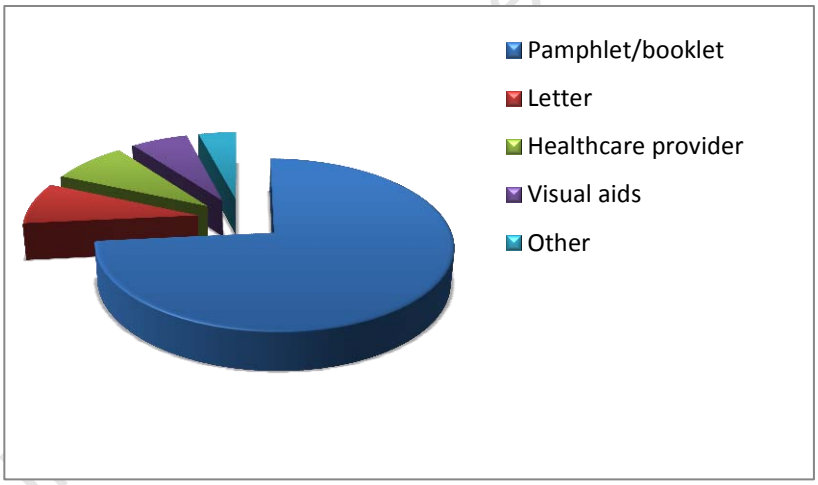

Figure 36: Information aids required by participants (n=80).

Dissemination of information: communication pathways

Participants also differed with respect to who notified the family about PT or screening appointments. Often family members were enlisted in this process, but some participants approached their partner (3.75%) or their local clinic sister (6.25%) (Figure 37).

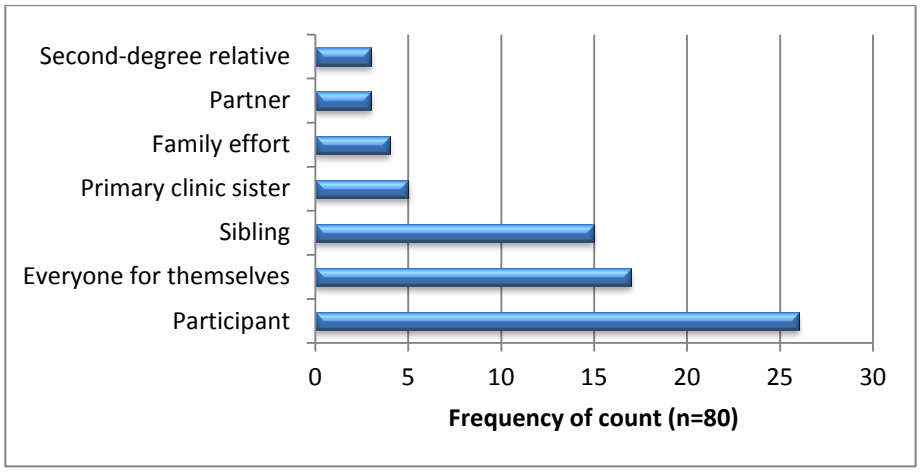

Figure 37: Communication pathways within Lynch syndrome families attending the GESC.

The majority (45/80) of participants were clear that the responsibility of informing relatives about their potential genetic risk should occur through the healthcare professional and not the family. Often families believe the responsibility lies with them, but they request a supporting role from their healthcare professionals (Aktan-Collan et al 2011; Forrest et al 2003). The preference for the healthcare professional is unusual and contradicts the findings of Bonadona et al (2002), Kerzin-Storrar et al (2002) and Segal et al (2004) who found their cancer (LS and HBOC) families favoured the family role when conveying information to their relatives. The different approach to communication may be a reflection of the low socio-economic status of the participants or the belief that the information may be more trustworthy if heard from a healthcare professional:

> ~~/~~../ the information will be better understood if it comes from the clinic, you know, how do I go about explaining…they do it so well there, rather the family hears it from them and can ask questions which will be answered rather than me trying to explain something which I have trouble understanding" (translated, male, 49 years).

> ~~/~~../ for example, if I told my cousin this news and tell her to go to the clinic, well, she would not listen to me but if someone from the clinic had to call her, then she would have to listen and she would be more likely to go as the information had come from the nurse or doctor" (translated, female, 38 years).

4.8 GENERAL HEALTH OF PARTICIPANT

Health-related behaviour and adapted lifestyle

Bowel-related concerns/symptoms subsequent to the participants' last attendance at the GESC were determined. Twenty-seven of the 80 participants (33.8%) reported that they had experienced problems during the interval between their last clinic appointment and the interview. When prompted to explain what they had done upon noticing the bowel symptoms, nine (33.3%) responded that they had seen a GP; eight (29.6%) had contacted a healthcare professional from the GESC; four (1.5%) told a family member/friend about their concerns, but did not contact any healthcare professional; and six (22.2%) did not contact anyone about their symptoms. Of concern is the fact that 37% (10/27) of participants did not discuss this issue with a healthcare professional. The lack of recognition of symptoms related to CRC (38.3% of participants could not identify any warning symptoms) may explain some of the participant's behaviour as seven of the ten (70%) who did not discuss their concerns with a healthcare professional had not been able to identify symptoms of CRC (Figure 23, page 144).

Several lifestyle behaviours, such as smoking and drinking, have been suggested to increase the risk of sporadic CRC malignancy (Giovannucci et al 1992; Willett et al 1990) and more recently, also of LS-related carcinogenesis (Diergaarde et al 2007; Pande et al 2010). The resultant influence and/change to the 80 participants' lifestyle, once counselled about being mutation-positive for the gene predisposing to LS, is presented in Table 59.

Table 59: Lifestyle risk behaviours of participants (n=80).

Category	Change to lifestyle related factor	Frequency	Percentage
Diet (eating habits)	Yes	16	20%
	No	64	80%
	Total	80	
Drinking habits (alcohol)	Yes-less	12	15%
	Yes-more	1	1.3%
	No	43	53.8%
	Never drunk alcohol	24	30%
	Total	80	
Smoking habits (cigarettes)	Yes-less	10	12.5%
	Yes-more	1	1.3%
	No	41	51.3%
	Never smoked	27	33.8%
	Total	80	

Some percentages may not add up to a 100% as a result of rounding-off.

In this cohort of participants, 15% and 12.5% of participants adopted health promoting lifestyles by reducing their alcohol consumption and cigarette smoking, respectively, and 20% by dietary changes. Participants who adapted their dietary habits (increased fruit and vegetable consumption and/or decreased red meat intake) were mostly unaffected (56.3%; 9/16) and female (62.5%; 10/16), with a mean age of 43.3 years (range, 31-53). Modified dietary habits were lower than those reported by Esplen et al (2001).

Decreased alcohol consumption occurred more frequently among affected participants (8/12). The average age of these 12 participants (six male and six female) with positive lifestyle behaviours, with respect to alcohol consumption, was 37.7 years (range, 24-46). A higher percentage of affected participants reduced their smoking habits (7/10 were affected with CRC) compared to unaffected (3/10) participants, which corroborates the findings of Burton et al (2010) who also found a lower prevalence of smoking among affected individuals. Six females and four males reported a reduction in their smoking habits. These ten participants were an average age of 44.9 years (range, 35-56).

The literature on changes to health behaviours (beyond that of compliance with colonoscopic or gynaecological screening guidelines) among individuals

with LS is scant. The prevalence of particular health behaviours or the effect thereof on tumour development, rather than the resultant adjustment to the behaviour, is typically described (Burton et al 2010; Diergaarde et al 2007; Pande et al 2009).

Psychological distress (DUKE-AD scale)

Psychological distress in individuals with LS is a reasonably well elucidated topic in the literature (Aktan-Collan et al 2001; Bonadona et al 2002; Broadstock et al 2000; Claes et al 2003; Claes et al 2005; Esplen et al 2003; Gritz et al 2005; Meiser et al 2004), though data for the SA LS population remains non-existent. Furthermore, no norm values are available for the general SA population, although a 12 month mental disorder study illustrated that the prevalence of psychiatric disorders was markedly higher in SA than other developed countries such as China, Germany, Italy and Japan (Williams et al 2008b). Table 60 represents the frequency of the ratings of the items in the DUKE-AD scale, which is capable of identifying clinical levels of depression and anxiety.

Table 60: Frequency of rating items of DUKE-AD scale (n=80).

Item	Description	Describes participant exactly (2)	Somewhat describes the participant (1)	Does not describe the participant at all (0)
F6a	Give up too easily	47 (58.75%)	23 (28.75%)	10 (12.5%)
F6b	Difficulty concentrating	44 (55%)	24 (30%)	12 (15%)
F6c	Comfortable around other people	54 (67.5%)	17 (21.25%)	9 (11.25%)
F6d	Trouble with sleeping	41 (51.25%)	24 (30%)	15 (18.75%)
F6e	Getting tired easily	45 (56.25%)	25 (31.25%)	10 (12.5%)
F6f	Feeling depressed or sad	40 (50%)	23 (28.75%)	17 (21.25%)
F6g	Nervousness	44 (55%)	17 (21.25%)	19 (23.75%)

The frequency of the ratings of the sum of the items of the DUKE-AD, among the 80 participants, is presented in Table 61.

Table 61: Frequency of rating the sum of each item of DUKE-AD (n=80).

Total score	Frequency	Percentage	Cumulative Percentage
0	8	10%	10%
1	9	11.3%	21.3%
2	17	21.3%	42.5%
3	8	10%	52.5%
4	7	8.8%	61.3%
5	5	6.3%	67.5%
6	4	5%	72.5%
7	6	7.5%	80%
8	6	7.5%	87.5%
9	2	2.5%	90%
10	5	6.3%	96.3%
11	2	2.5%	98.8%
13	1	1.3%	100%
Total	80	100%	

Eight participants (10%) claimed to have no symptoms of anxiety or depression (score of 0 on DUKE-AD). When considering gender, six of the eight participants were male (75%). Only two of these participants had a previous cancer, however in both cases, the malignancy had been identified early without the involvement of metastases. These eight individuals were adherent to screening guidelines, with one participant in Group 1 (no missed colonoscopies) and the remaining seven in Group 2 (having missed only one colonoscopy).

The highest total score was 13 (out of a possible 14), reported by a female participant who had a total colectomy with ileorectal anastomosis at the age of 31 years (for an adenomatous polyp). She was mostly compliant with screening guidelines (Group 2). The mean score of the items on the DUKE-AD scale was 6 (SD=3.3).

Parkerson and Broadhead (1997) suggested the following interpretation of the overall scores (Table 62).

Table 62: Interpretation of overall scores on DUKE-AD (Pakerson and Broadhead 1997).

Total Score (sum of items)	Description of score
1 – 5	No excessive symptoms of anxiety and depression
>5	Excessive symptoms of anxiety and depression

Application of the key, identified excessive symptoms of anxiety and depression in 32.5% of participants (Table 63). These findings are significantly higher than that of other LS studies where minimal adverse psychological effects were observed (Bonadona et al 2002; Esplen et al 2001; Esplen et al 2007; Liljegren et al 2004). Williams et al (2008b) suggest that the SA population may be at a higher risk of mental disorders due to the dynamics of the country. Prior to 1994 this included racialised policies and the victimisation of the anti-apartheid struggle and following this era, the high rates of crime and violence, poor economic circumstances and burden of HIV/AIDS in SA.

Table 63: The number of individuals with excessive symptoms of anxiety and depression (n=80).

Total Score (sum of items)	Description	Frequency	Percentage	Cumulative Percent
1 – 5	Not Excessive	54	67.5%	67.5%
>5	Excessive	26	32.5%	100%
	Total	80	100%	

The cohort of individuals reporting excessive symptoms of anxiety and depression, comprised 88.4% (23/26) females, which is generally in accordance with international findings of females illustrating higher levels of depressive symptoms and anxiety than males (Broadstock et al 2000; Esplen et al 2003; Meiser et al 2004). The mean age of the 26 participants was 40.8 years and these individuals were largely unaffected with CRC (13/26). The average adherence group among the participants was Group 3 (missed two colonoscopies) and the mean number of FDR with cancer 1.7. Fifty-seven percent (15/26) of participants with excessive symptoms conveyed a high-inevitable personal CRC lifetime risk (Table 64).

Table 64: Characteristics of participants with excessive symptoms of anxiety and depression (n=26).

Participant (P)	Gender	Age	Affected (A)/ Unaffected (U)/ Polyp (P)	Adherence group	Perceived lifetime risk of CRC development	Affected parent	Number of affected siblings	Number of affected children	Total (Number of parents, siblings and children with CRC)
P3	M	50	A	1	Operated-low risk	Father	2	0	3
P8	F	39	P	2	Operated-low risk	-	3	0	4
P10	F	47	A	2	Operated-low risk	Father	0	0	1
P14	F	49	U	5	High	-	1	0	2
P19	F	24	U	5	Inevitable	Father	0	0	1
P29	F	27	U	1	High	Mother	0	0	1
P31	F	56	U	5	Does not know	Mother	0	1	2
P35	F	49	P	5	Regular scopes-low risk	Father	0	0	1
P40	F	55	P	5	Regular scopes-low risk	Father	1	0	2
P41	F	47	A	2	50%	Mother	0	0	1
P42	F	37	U	3	50%	Mother	2	0	3
P43	F	29	U	3	High	Mother	0	0	1
P49	F	38	A	5	Inevitable	-	0	0	0
P55	F	24	U	1	Very high	Father	0	0	1
P56	M	43	U	1	Very high	Mother	1	0	2
P57	F	53	P	3	High	Mother	0	0	1
P59	F	50	P	2	Operated-low risk	-	1	0	1
P60	F	27	P	5	Very high	Mother	0	0	1
P61	F	38	A	2	Inevitable	Father	1	0	2
P62	F	33	U	5	High	Mother	0	0	1
P67	F	52	U	5	Very high	Mother	1	1	3
P74	F	22	U	5	High	Father	0	0	1
P76	F	34	U	1	50%	Father	0	0	1
P77	F	38	P	1	Very high	Father	0	0	1
P81	F	54	U	1	Inevitable	-	5	0	5
P82	M	47	A	5	Operated-low risk	Mother	1	0	2

Van Oostrom et al (2007) recognised that individuals, entering into PT, who experienced a parental cancer in their childhood (<13 years) or lost a parent to cancer during this age period, were more vulnerable to psychological distress. The data from this analysis confirms greater distress in individuals experiencing parental cancer during their childhood (≤12 years). The number of participants with excessive symptoms per age group (childhood, adolescence, adulthood) is illustrated in Table 65.

Table 65: Number of participants with excessive symptoms per age group (n=26).

		DUKE-AD Score			Total
		Not excessive	Excessive	Percentage	
Earliest memory of parental cancer	≤ 12 years	13	9	69.2%	22
	13-18 years	11	5	45.45%	16
	> 18 years	24	11	45.83%	35
	Parent not affected	6	1	16.67%	7
Total		62	26		80

The nine participants exposed to a parental cancer in childhood with excessive symptoms were mostly female (7/9). The parent with cancer had died from the malignancy in all cases. Forty-four percent (4/9) of these participants defined their perceived lifetime CRC risk as ‗high' or ‗inevitable'.

Cancer Worry Scale (CWS)

The CWS was used to determine social role dysfuntioning relating to distress about developing cancer. Participants' responses, based on the four-point scale, ranging from ‗not at all/rarely' to ‗almost all the time', are presented in Table 66.

Table 66: Frequency of rating items of the CWS (n=80).

Item	Description	Not at all/ rarely (1)	Sometimes (2)	Often (3)	Almost all the time (4)
F7a	How often have you thought about your own chances of developing cancer?	35 (43.8%)	18 (22.5%)	20 (25%)	7 (8.8%)
F7b	How often have you worried about your own chances of developing cancer?	40 (50%)	18 (22.5%)	16 (20%)	6 (7.5%)
F7c	How often has thoughts about getting cancer affected your mood?	61 (76.3%)	8 (10%)	8 (10%)	3 (3.8%)
F7d	How often have thoughts about getting cancer affected your ability to perform daily activities?	66 (82.5%)	7 (8.8%)	6 (7.5%)	1 (1.3%)

The impact of cancer worry on mood (F7c) and performance (F7d) was low. Ten percent of participants described mood interference occurring ‗often' and 3.8% ‗almost all the time'. The frequency of responses on performance (F7d) indicated that 7.5% of participants felt that cancer worry affected their daily activities ‗often' and for 1.3% of individuals interviewed the effect occurred ‗almost all the time'.

The results of a two-dimensional CAT-PCA, explained 90% of the total variance. Table 67 presents the component loadings of the four items of the CWS.

Table 67: Component loadings per item of a two dimensional CAT-PCA.

Items		Dimensions	
		1	**2**
F7a	How often have you thought about your own chances of developing cancer?	0.782	0.542
F7b	How often have you worried about your own chances of developing cancer?	0.840	0.426
F7c	How often has thoughts about getting cancer affected your mood?	0.843	- 0.462
F7d	How often have thoughts about getting cancer affected your ability to perform daily activities?	0.837	- 0.468

The responses to the four items were treated at an ordinal level and the plot of the category scores of the two-dimension CAT-PCA shows that the

categories ‗often' and ‗almost all the time' are projected close to each other and form one extreme pair of vectors. The category ‗rarely' represents the opposite extreme and ‗sometimes' is located more or less in middle of the vectors (Figure 38). The first dimension is determined by F7a (thoughts) and F7b (worries) and the second dimension by F7c (mood) and F7d (daily activities/performance). This illustrates that participants differentiate between ‗thoughts' and ‗worries' about cancer and having these ‗thoughts/worries' affect their ‗moods' and ‗behaviour'. The relatively long vector of item F7d (effect on daily activities) is caused by the single (outlier) patient that claimed to be ‗highly affected' in his performance. The response pattern deviates significantly from those of the other participants. P46 is an asymptomatic 31 year old male who missed two colonoscopic appointments and had a 50% score on ‗knowledge'.

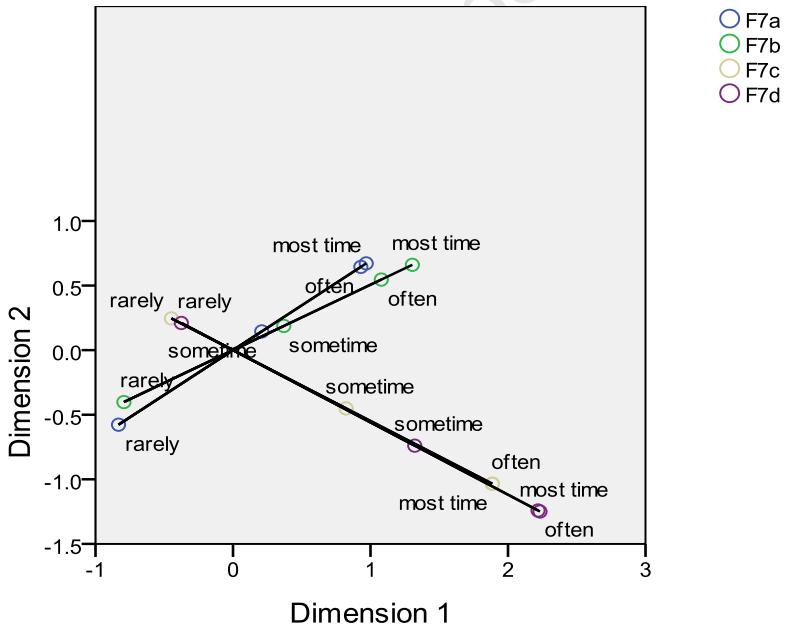

Figure 38: Plot of category points of the four items (F7a-F7d) on CWS.

A two-dimensional analysis with items about ‗knowledge' and ‗adherence', added to the items of the CWS, resulted in a fit that explained almost 68% of the total variance. Figure 39 shows that ‗knowledge' and ‗adherence' were not

related to ‗thoughts' or ‗worries' about risks nor did it illustrate any effect on ‗mood' and ‗performance'.

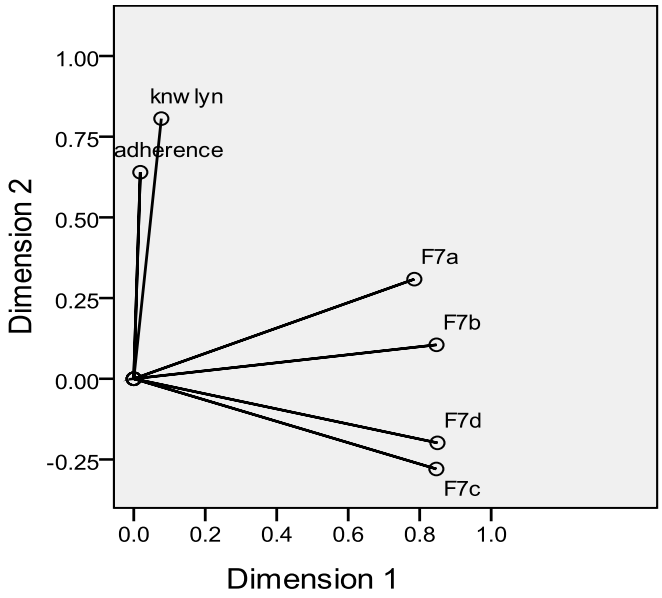

Figure 39: A plot of the component loadings of the four items (F7a-F7d) combined with ‗knowledge' and ‗adherence'.

The effect of exposure to cancer (the number of FDR with cancer) on the CWS score (specifically the effect on ‗thoughts/worries' and ‗mood/performance') was determined. The re-coded CWS items are displayed in Table 68 for the purpose of transparency:

Table 68: Re-coding of rating items on the CWS to reflect the two new variables (thoughts/worries and mood/performance).

		Re-coded description			
		Rarely	Sometimes	Often	Almost all the time
F7a + F7b	Thoughts/ Worries	2=1	3,4=2	5,6 =3	7,8=4
F7c + F7d	Mood/ Performance	2=1	3,4=2	5,6 =3	7,8=4

Table 69 indicates that more respondents than expected have less thought disturbances about cancer when two to six of their family members are affected by cancer, and more respondents than expected have more thoughts about cancer when none or one member of their family is affected (0 or 1),

although the pattern is not strong enough to reach statistical significance: p=0.18 (ChiSq = 3.42, 2)

Table 69: Cross-tabulation of cancer-related thoughts with number of first-degree relatives with cancer.

			Thoughts (7a and 7b on CWS)			Total
			Not at all/ rarely	Sometimes	Often	
FDR with cancer	Few affected (0-1 family members)	Count	12	10	18	40
		Expected Count	16.0	9.0	15.0	40.0
	Many affected (2-6 family members)	Count	20	8	12	40
		Expected Count	16.0	9.0	15.0	40.0
Total FDR with cancer		Count	32	18	30	80
		Expected Count	32.0	18.0	30.0	80.0

The re-coded category _Almost all the time' (7,8=4) received no responses and is not listed as a category.

The relationship between mood and the number of affected family members with cancer appears more explicit. Table 70 shows a trend (lowest expected value in cell was 4.5) that respondents with many affected family members were less affected by mood than expected whereas, respondents with few family members affected were more affected by mood than expected: p=0.052 (ChiSq=5.92, 2).

Table 70: Cross-tabulation of mood disturbances with number of first-degree relatives with cancer.

			Mood affected (7c and 7d on CWS)			Total
			Not at all/ rarely	Sometimes	Often	
Total FDR	Few affected (0-1 family member)	Count	26	6	8	40
		Expected Count	30.5	4.5	5.0	40.0
	Many affected (2-6 family affected)	Count	35	3	2	40
		Expected Count	30.5	4.5	5.0	40.0
Total		Count	61	9	10	80
		Expected Count	61.0	9.0	10.0	80.0

The re-coded category _Almost all the time' (7, 8=4) received no responses and is not listed as a category.

The pattern becomes stronger if mood is dichotomised into _rarely' and _sometimes/often' (p=0.018; ChiSq=5.591, 1). It could be speculated that

exposure to cancer may create a familiarity with the disorder and as such, have less of an impact on cancer worry.

Table 71 shows that ‗thoughts/worries' about cancer rather than ‗mood/performance' affects both the 64 unaffected participants and the 16 participants who developed cancer.

Table 71: Frequency of cancer-related thoughts and mood disturbances among affected (n=16) and unaffected (n=64) participants.

			No cancer		Cancer	
Item	Description	Score	(n=64)	Percentage	(n=16)	Percentage
F7a + F7b	Thoughts/ worries affected	Not at all/rarely	59	39.1%	15	46.9%
		Sometimes	28	21.9%	8	25%
		Often	41	32%	9	28.1%
F7c + F7d	Mood/ performance affected	Not at all/rarely	99	77.3%	28	87.5%
		Sometimes	13	10.2%	2	6.3%
		Often	16	12.5%	2	6.3%

4.9 RESEARCH

The frequency and experience of involvement in research studies was determined and is shown in Table 72.

Table 72: The nature and frequency of the involvement in longitudinal and cross-sectional research studies.

		Frequency	Percentage
Involved in longitudinal studies	Yes	20	25%
	No	60	75%
	Total	80	100%
Involved in cross-sectional studies	Yes	29	36.3%
	No	51	63.7%
	Total	80	100%
Participate in future studies	Yes	59	73.8%
	No	10	12.5%
	Ambivalent	6	7.5%
	On condition	5	6.3%
	Total	80	100%

Overall, the majority (73.8%; 59/80) of participants welcomed involvement in future research. The additional contact(s) with the healthcare professionals,

as a result of being involved in a research study, was acknowledged as an added benefit. A desire to help others or to aid the understanding of the cancer served the participants with a sense of altruistic purpose:

> Oh, it was definitely worth it, I feel like I made a difference, like I really helped the doctor's understand this condition /…/ if it can help me or even those who come after me, that will be great" (translated, male, 35 years).

The 12.5% (10/80) of participants who declined future involvement in forthcoming research studies were mostly female (9/10) and declined to participate as a result of the side-effects of the medication used during their trial involvement. The majority of these participants (80%) were involved in longitudinal research studies (80%). Eight participants (10%) were ambivalent about the experience and five (6.3%) expressed that specific criteria had to be met prior to re-involvement: research feedback, preference for shorter study period, direct benefit, exclusion of trials with side-effects. A negative experience with research has been reported previously, however, as in this study it always occurred in the minority (Collins et al 2000; Stadler et al 1998).

4.10 SUMMARY OF RESULTS/FINDINGS FOR GROUP A

Although the majority of participants (90.2%) were satisfied with their experience and the services offered by the GESC, more male participants were found to have questions unanswered and struggle with the understanding of the inherited risk of LS compared to their female counterparts. The level of knowledge of LS was poor among individuals within Group A (average of 6.5 out of 11 on the Domanska scale) and areas less clearly understood related to the genetic aspects of LS. While information on LS was almost exclusively gained from the GESC and most participants did not seek further information, only half of the individuals interviewed had access to an additional information source. A low knowledge score related to

a shorter period within the programme while greater knowledge appeared to increase with length of time in the GESC.

One of the recognised benefits of the GESC is that individuals presenting for screening or PT, not only have access to a free service, but additionally a free ambulance transport system (from their local clinic to the GESC). As transportation barriers are often implicated in adherence studies, it was not expected to materialise as a barrier to surveillance, among the group of participants attending the GESC. Despite this, participants with the most missed colonoscopic appointments travelled for longer than one hour and used the free ambulance transport services to the GESC. Most of these participants were female and over the age of 50 years. The concerns with this free service were found to relate to minimal toilet breaks and perceived reckless/dangerous driving.

Ninety-three percent of participants had attended some form of surveillance, however, less than a quarter of participants were adherent with all their recommended colonoscopies. Rates of compliance differed when comparing self-report to calculated uptake rates. Typically, over-estimation in the adherence category (Group 1) and under-estimation in the non-adherence categories (Group 2-5) occurred.

The experience of the colon preparation was recognised as the most difficult part of surveillance. Unfortunately, preparation precedes screening and if not carried out successfully, inhibits the completion of the screening process due to the inability to visualise the bowel. Simply changing the type of preparation mixture, to that of the participant‘s preference, could facilitate a more positive preparatory experience. Although certain participants found the procedure painful, the pain associated with colonoscopy was recognised to decrease over time.

One avenue that had to be explored in this study was that of the available amenities to the participants, particularly in light of its necessity in the preparation process and the knowledge that these facilities are usually below standard in developing countries. The number of participants with access to an indoor flushable toilet is far below that of the general population in the WC and NC. Almost a quarter of participants had to make use of an ‗outside toilet', which exposed them to the elements of the winter weather and a lack of privacy associated with frequent toilet use.

Although facilitators to adherence were similar to those previously described in the literature, barriers unique to the GESC were identified and suggestions to address these barriers have been implemented and are further discussed under Recommendations in Section 6.1. A relationship between the age of the participant and non-adherence was identified. The youngest age group had the least number of missed colonoscopies, whereas the older age groups had a higher surveillance absence rate.

The majority of participants disclosed their genetic test result on the same day that they had received the information from the healthcare professional at the GESC. Disclosure occurred when a participant was emotionally close to a particular person or when trying to engage other family members into PT. Unfortunately the implications of the test result were not always discussed with the at-risk family members, even if disclosure of their personal result had occurred. Simply sharing results did not always include the discussion of the familial risk and availability and benefit of PT for family members. There was some evidence indicating that females and affected participants were key messengers in discussing genetic risk within the family. The calculated uptake rate among the nuclear family including siblings and eligible children (over the age of 18 years) was 97% and 73.6% respectively.

Of interest, is that more participants approved of the idea that the healthcare provider, rather than the family, should inform their relatives about the

potential genetic risk. This view contests the findings from other published studies, highlighting the belief that information may be valued as more trustworthy if presented by a healthcare professional, especially in an environment associated with a low socio-economic context. Moreover, the difficulty of conveying information if its implications are less clearly understood by the participant themselves is highlighted.

Greater psychological effects, when compared to other LS studies in developed countries, were identified within the cohort, and excessive symptoms of anxiety and depression occurred in 32.5% of participants. As norm scores are not available for the general SA population, a comparison could not be made and the psychological distress could be present as a result of higher population levels. Another explanation could relate to the high number of females within the study cohort (generally associated with higher levels of depressive symptoms than in males). The subgroup which exhibited the greatest excessive symptoms of distress comprised mainly unaffected females.

When considering the CWS, those participants with a greater number of affected family members, had cancer-related thoughts (p=0.18) and mood (p=0.052) affected less often. Although this pattern was not strong enough to reach statistical significance it does suggest that under-exposure rather than over-exposure to the familial cancer, is a potentially important predictor of distress in individuals with LS.

4.11 GROUB B - PREDICTIVE GENETIC TESTING PROGRAMME (PT)

The protocol for PT for LS (Appendix 1) was developed in 1996/1997 shortly after genetic testing became available in SA. Typically, the PT programme involved two sessions with a genetic counsellor: (1) discussion of information

and implications of LS and testing (if requested); and (2) delivery of results with enrollment into appropriate medical management, if required.

A total of 33 individuals underwent the PT programme offered by the Division of Human Genetics, University of Cape Town and Division of Colorectal Surgery, Groote Schuur Hospital during the 18 month recruitment period, from June 2009 to December 2010. Genetic testing included direct mutation analysis and restriction enzyme digest on DNA derived from venous blood (Ramesar et al 2000).

All 33 participants consented to being interviewed to evaluate the genetic counselling and PT programme (100%), however, data analysis was limited to a subset of 23 (69.7%) from the second interview and 22 (66.%) from the third interview. The difference in numbers, between the second and third interview occurred because one participant selected to discontinue with certain sections of the interviewing process after having a sister die from CRC during this period. The drop-out rate was strongly determined by the number of participants who did not return to receive their genetic test result (10 participants). Where possible, these individuals were contacted to investigate the reasons for dropping out to ensure that they were not relevant to the evaluation of the genetic testing and counselling programme. The reasons given were: ‗to wait until another family member had to enter into PT and then go to the GESC at the same time'; ‗work/studying made attendance at the result-giving appointment difficult'; ‗relocation to a different province with intent to return at a later stage'; and ‗transport problems associated with the distance to GESC'.

All the primary and secondary interviews were conducted in a private office at either the outreach or hospital GESC, immediately after the initial genetic counselling and testing session. The majority (51.5%) of the third interviews took place at the homes of the participants. The rest of the participants preferred to be seen away from their home and alternate venues were

arranged near the participants‘ residence, place of employment or a private room at their local clinic.

Three participants (9%) complained of bowel-related symptoms at the time of their first visit. Colonoscopies were scheduled for all three participants. The procedures occurred subsequent to the PT result session for two and prior to the result session for one participant. The outcome of the endoscopic procedures were normal in two cases. In one participant a large adenomatous polyp (> 5cm) was identified and surgically removed.

4.12 DEMOGRAPHIC DATA AND PERSONAL HISTORY

The characteristics of the participating sample in Group B are illustrated in Table 73.

Table 73: Sociodemographic characteristics of the PT study participants (n=33).

Participant characteristics	PT group (Group B)	
	n	Percentage
Gender		
Female	15	45.5%
Male	18	54.5%
Age (years)		
18-19	10	30.3%
20-29	11	33.3%
30-39	5	15.2%
40-49	3	9%
50-59	3	9%
≥60	1	3.7%
Ethnic group		
Mixed Ancestry	25	75.8%
White	8	24.2%
Marital status		
Married/partner/relationship	8	24.7%
Single/divorced/widowed	25	75.8%
Home language		
Afrikaans	23	67.7%
English	9	27.3%
English and Afrikaans	1	3.7%
Province		
Northern Cape	6	18.2%
Western Cape	27	81.7%
Residential area		
Urban	28	84.7%
Rural	5	15.2%

The cohort comprised 18 males (54.5%) and 15 females (42.2%) with a mean age of 28.7 years (range, 18-61 years, SD=12.7). Most participants were of Mixed Ancestry (75.8%) and spoke a home language of Afrikaans (67.7%). Twenty-four percent reported themselves to be in a relationship. In contrast to Group A, more participants frm Group B were from the WC (81.7%) and residing in an urban area (84.7%). The low number of recruited individuals from the NC would have been partly as a result of the limited PT opportunities, usually only offered annually at the outreach GESC. The

average age that participants entered into PT was 28.7 years. This is somewhat late considering PT is offered from 18 years of age in this setting.

Level of education

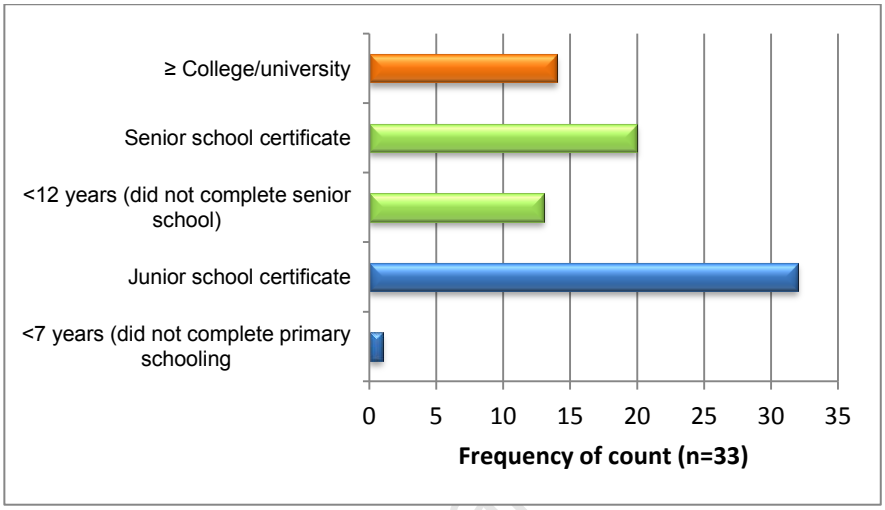

Figure 40: Level of education among participants entering into PT.

Eleven percent of the general population of the WC and 6.1% of the NC have some form of tertiary education (Statistics South Africa 2005). In this cohort, 42.1% (14/33) had enrolled for higher education, which is consistent with other reports suggesting that individuals undergoing PT for LS have a higher education level than those from the general population (Aktan-Collan et al 2000; Codori et al 1999). The main reasons provided for not progressing from secondary school to tertiary education include: parents financial constraints (15%), care required at home as a result of a parent with cancer (15.2%) and for 12.1% social circumstances (including involvement in a gang, expulsion or failing at school).

Employment and occupation

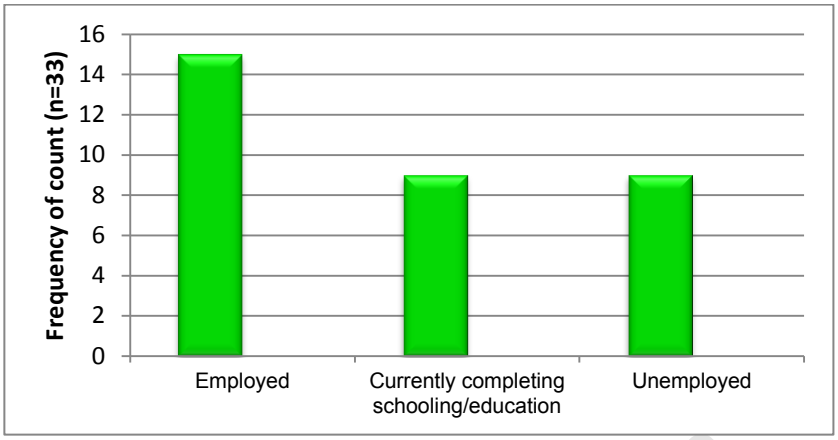

Figure 41: Employment and unemployment rates among participants entering into PT (n=33).

Only 27.3% (9/33) of participants from Group B were unemployed, which was significantly lower than that of Group A (67.3% outreach versus 39.2% hospital). The inclusion of students within the employment stratification (27%) may have accounted for this low rate. Of the 15 participants who were employed, 46.7% were involved in the managerial or professional sector (Table 74). This is much higher than the rates reported for the outreach (7.7%) and hospital clinic of Group A (28.5%).

Table 74: Occupation categories for participants entering into PT (n=33).

Occupation	Frequency	Percentage
Managerial, professional, semi-professional	7	21.7%
Clerical, sales, service	2	6.1%
Skilled agriculture, craft, operations	3	9.1%
Elementary occupations	4	12.1%

Income

The mean monthly household income for the PT participants was R10 700 (USA$ 1 551) (category: R6 401-R12 800). The total income per household of the 33 PT participants appears in Figure 42.

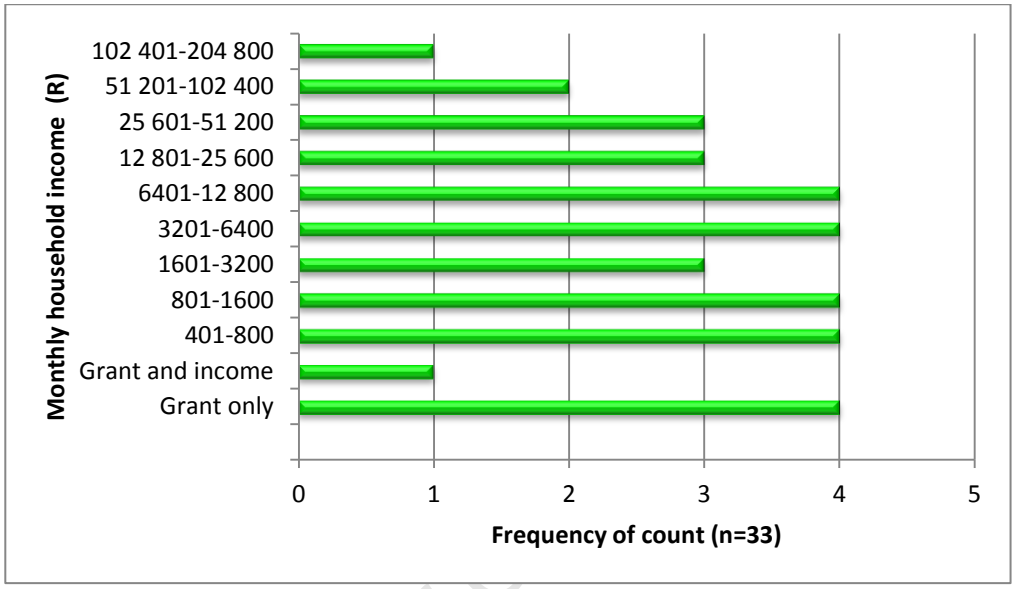

Figure 42: The level of household income for the PT participants (n=33).

Four participants (12.1%) were from a household which received an income from government grants only. Two of these households held dual grants (All-Pay and child support grant), the other two lived off pension (old age grant) and child support grants. The highest number of occupants within one household was 15, the mean number of individuals per household was 4.5 persons.

Family history and exposure to Lynch syndrome

Twenty-one (63.3%) participants had an affected parent of which 42.1% were paternal and 21.2% maternal. Thirteen (62%) of these parents had died of CRC. The mean age of participants, at the age that their parent had been diagnosed with cancer, was 20.3 years.

All 33 participants had been exposed to CRC by virtue of affected FDR(s) (Figure 43).

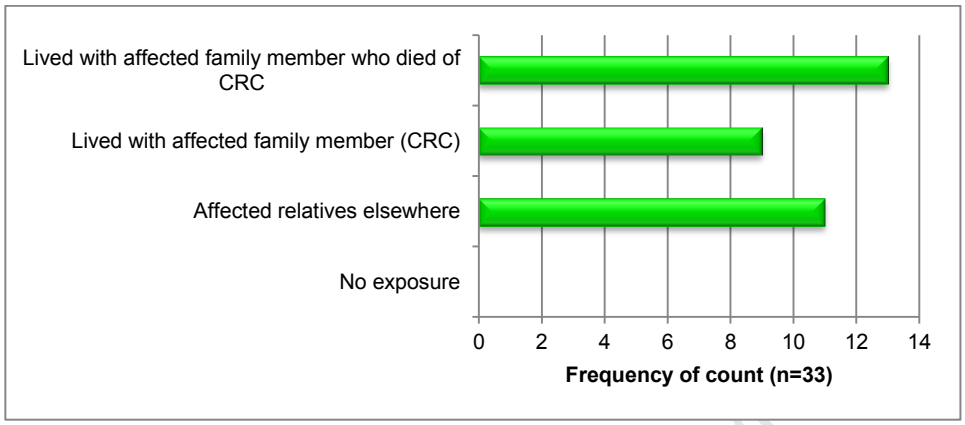

Figure 43: Exposure to colorectal cancer (CRC) within family.

Predictive testing uptake in the family

The number of siblings and children per participant appear in Table 75. The mean number per participant was 3.1 and 1.8 respectively.

Table 75: Number of siblings and children per participant (n=33).

Count								
	0	1	2	3	4	5	8	≥ 9
Siblings	2	8	8	4	2	7	1	1
Children	24	3	5	1	-	-	-	-

For seventeen participants (51.5%), the uptake rate among all eligible siblings was 100%. Ten participants (30.3%) had some siblings (but not all eligible siblings) enter the PT programme. Four participants (12.1%) had none of the eligible siblings, beyond the participant themselves, enter into PT. Siblings were either too fearful of testing or had a misconception about the type of information obtainable from PT:

–They are scared, more scared than anything, I guess they are aware of the risk but that is not enough to make them come" (female, 32 years).

"My brother say's that he will not let them take out his colon, I guess he refuses to come because he thinks they will find cancer and then want to operate on him, like they did with dad. We have tried to explain the test, like [genetic counsellor] said, the test is just something that tells you about your chance of getting it…but he has made up his mind" (female, 18 years).

Some participants believed their siblings would come for PT, but that the right time would have to present itself:

"Well, I know they will come, this is very important for our family. Now that we know about the fault in our DNA…I know that [genetic counsellor] said that [X], she is in Australia and my other sister [Y], who is in London can get the test done through their respective hospitals, but I guess they are waiting for the right time…I know [X] has thought about doing it here at home when she comes out to visit again, you know so that the family are all here /…/ I guess it is just easier when you are comfortable, you know, familiar…" (male, 38 years).

Family planning and attitude to termination of pregnancy

Prior to the first PT interview, nine participants (27.3%) had one or more children (Table 76). The participants' responses to termination of pregnancy (TOP) if the (future) fetus were mutation-positive for LS are presented in Figure 44.

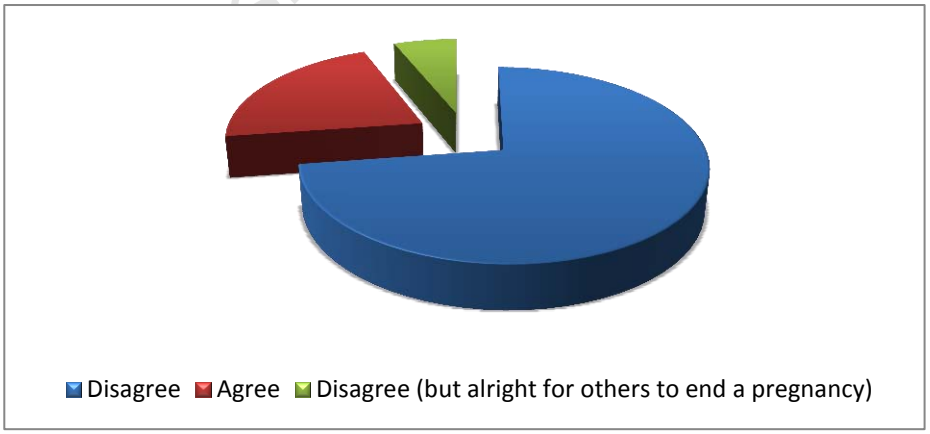

Figure 44: Attitude to termination of pregnancy (TOP) in mutation-positive fetus.

The majority (72.7%) of participants did not agree with TOP due to moral and/religious views (79.2%) and surprisingly only four (16.7%) did not favour the concept of TOP due to preventative management, for CRC, being

available for LS. One participant (4.2%) did not consider termination as an option as he and his wife had been struggling to conceive. Dewanwala et al (2011) found that 42% of individuals entering into PT for LS would consider prenatal testing in a future pregnancy. However, the consideration of a TOP, if prenatal testing identified a disease-causing mutation, was not investigated. Prenatal testing for LS remains a contentious issue due to the late-age of onset, incomplete penetrance and relatively effective cancer prevention programmes including endoscopic screening and prophylactic surgery. Even if chorionic villi sampling or amniocentesis is offered, uptake is expected to remain low (Aronson et al 2009; Offit et al 2006; Raymond et al 2009). To date, no cases of prenatal testing and selective termination have been identified for LS within the tertiary hospital centres in the WC and NC province (Ruppelt 2011; Vorster 2011).

4. 13 GENETIC COUNSELLING PERSPECTIVES AND SATISFACTION

Aspects of the genetic counselling and PT session which held particular salience for participants are displayed in Table 76.

Table 76: Rating frequencies per item of information discussed during genetic counselling (n=33).

	Items	Very important (1)	Important (2)	Not important (3)
		1	**2**	**3**
1a	Cause of the condition (LS)	27	2	3
1b	Explanation on why the condition is passed on from one generation to the next	21	9	3
1c	The medical name for the condition	17	13	3
1d	Explanation on who else is at-risk (in the family) for LS	24	9	-
1e	If treatments are available for LS	28	5	-
1f	Potential treatments that may become available in the future	29	4	-
1g	Information on what will happen to someone with the condition as time goes by	26	7	-
1h	Availability of a genetic test to see if I will get the condition	29	4	-
1i	To be able to contact other families affected with the condition, for support	18	7	8
1j	The information covered during the session should be written down for future reference	21	10	2
1k	Is there a test for this condition in pregnancy	22	7	4

The information most valued by participants related to four specific domains. These included: cause (27/33; 81.7%), recognition (26/33; 78.8%), testing (29/33; 87.8%) and treatment of LS (29/33; 87.8%).

Satisfaction with genetic counselling

Table 77: The rating frequencies per item on the genetic counselling satisfaction scale (n=33).

Items		Strongly disagree (Unsatisfactory)	Somewhat agree (Somewhat satisfactory)	Strongly agree (Highly satisfactory)
B3a	The staff member at the clinic seemed to understand the stress I was facing	1	8	24
B3b	They helped me to identify what I needed to know to make a decision about the blood test and surveillance	1	3	29
B3c	Felt better about my health after meeting with them	2	9	22
B3d	The session was about the right length of time	2	4	27
B3e	They were truly concerned about my well-being	1	4	28
B3f	The session was valuable to me	1	3	29
	Total	8 (4%)	31(15.7%)	159(80.3%)

Overall 80.3% of participants were highly satisfied with the genetic counselling they received. Fifteen percent were moderately satisfied (selected somewhat satisfactory) and only 4.7% were unsatisfied. Figure 45 shows a graphical representation of the frequency of each item that was marked as ‗highly satisfactory' (strongly agreed).

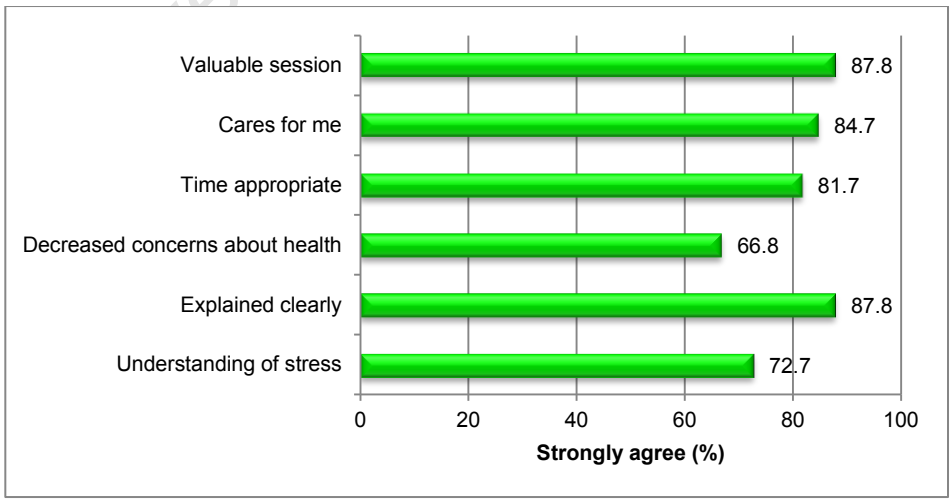

Figure 45: Satisfaction with the process and content of genetic counselling according to the genetic counselling satisfaction scale (n=33).

The majority of participants felt that the information had been presented clearly (87.8%), that the counselling had been valuable to them (87.7%), and that the counsellor cared about them (84.7%). The length of the session was appropriate for 81.7% of participants. Despite most of the items rating as ‗highly satisfactory', only 66.8% of participants indicated that their health-related concerns had been decreased and 71% reported that the counsellor had understood the stress with which they were faced.

Figure 46 displays the total satisfaction score per participant (n=33). The average score among the participants was 16.6 out of a possible 18 (SD=2.2). The participant with the lowest score (7/18) was male, currently attending tertiary education and of White ancestry.

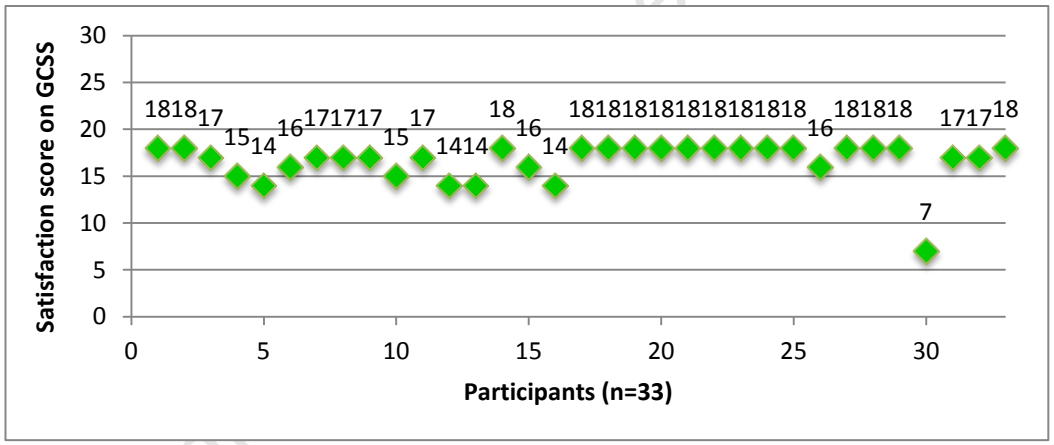

Figure 46: Total score per participant on the genetic counselling satisfaction scale.

Generally, participants reported a high level of satisfaction with their genetic counselling session, with most of the responses at the top end of the satisfaction scale (Table 77). This finding is in line with previous reports of satisfaction (76%-89%) in individuals attending cancer genetic counselling in familial cancer clinics (Davey et al 2005; Kausmeyer et al 2006; Nordin et al 2002; Stadler and Mulvihill 1998); in colorectal cancer clinics (Collins et al 2000) and in breast cancer clinics (Bober et al 2007; Charles et al 2006; Tercyak et al 2004).

Table 78 presents those variables which were selected to be of relevance to the differentiation in response to the level of satisfaction with the genetic counselling scale. The analysis was conducted on all 33 participants. Data was collected on five demographic variables and the six questions on satisfaction were rated on a semantic three-point scale.

Table 78: Demographic variables used in the analysis of the level of satisfaction with genetic counselling (n=33).

Item	Category	
Gender	19 (Male)	14 (Female)
Age	21 (below mean age of presenting for PT)	12 (above mean age of presenting for PT)
Ethnic group	25 (Mixed Ancestry)	8 (White)
Secondary education	20 (completed secondary schooling)	12 (did not complete secondary schooling)
Tertiary education (college)	15 (attended)	18* (Did not attend)

*One participant was in the process of completing secondary schooling.

The component loadings of the two-dimensional CAT-PCA are presented in Table 79.

Table 79: Component loadings per item of a two-dimensional CAT-PCA involving participant demographics and the genetic counselling satisfaction scale (n=33).

Items	Demographic information	Dimensions	
		1	**2**
A3	Ethnicity	-0.480	-0.576
A6b	Senior schooling	-0.297	-0.856
A6c	College (Tertiary education)	0.336	0.806
	Genetic Counselling Satisfaction scale		
D3a	The staff member at the clinic seemed to understand the stress I was facing	0.964	-0.176
D3b	They helped me to identify what I needed to know to make a decision about the blood test and surveillance	0.964	-0.181
D3c	Felt better about my health after meeting with them	0.351	-0.197
D3d	The session was about the right length of time	0.810	0.010
D3e	They were truly concerned about my well-being	0.965	-0.179
D3f	The session was valuable to me	0.967	-0.173

The variables ‗gender' and ‗age' had values that did not associate with any other variables. As a result, these two variables did not explain more than their own variance and were removed from the analysis.

The results of a two-dimensional categorical analysis CAT-PCA with the demographic variables treated as nominal and the satisfaction ratings as ordinal are shown in Figure 47. The eigenvalues for the dimensions were 4.96 and 1.99 respectively, explaining a total variance of almost 70%.

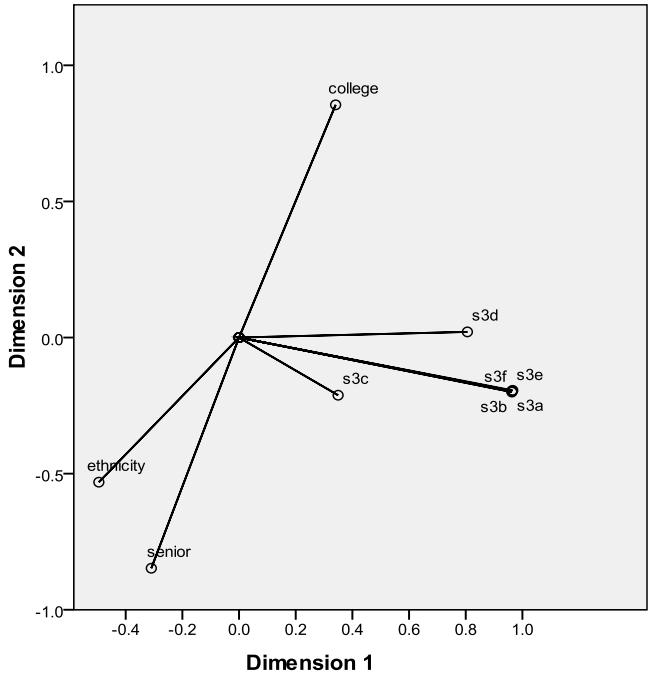

Figure 47: A plot of the component loadings of the demographic variables and the six items (3a-3f) on the genetic counselling satisfaction scale.

Figure 47 shows the mutual association between the items in relation to each dimension after normalisation. Two main clusters appear: education and satisfaction. Considering the first cluster, ‗college' (tertiary education) and the mirror image of the item ‗senior' (completed senior schooling) are related and contribute relatively strongly to dimension two. Item ‗ethnicity' contributes almost equally to both dimension one and two. The contribution of gender and age is small and explain less than their own variance. Removal of these variables results in a better fit and does not affect the projections (76.4% explained variance).

The plot of the category scores of education suggests that more White than Mixed Ancestry participants completed their studies (Figure 48).

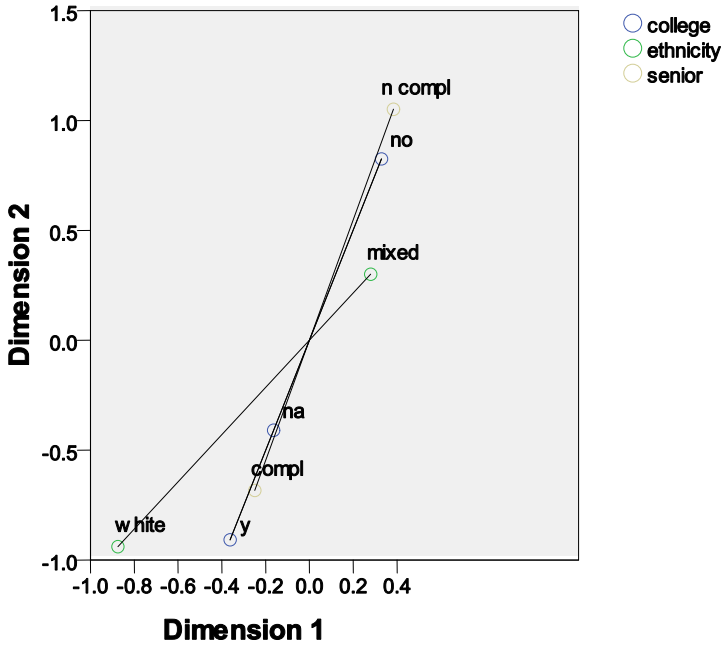

Figure 48: A plot of the component loadings of the items education and ethnicity. n compl = not completed. compl = completed. Na = not applicable as still attending senior schooling.

The second cluster is formed by the items of the genetic counselling satisfaction scale (3a-3F) (Figure 47). The plot of the category points suggests that items 3a, 3b, 3e and 3f are strongly related and contribute significantly to dimension one. The close projection of these items indicates that the ‗session was viewed as valuable' if the participant perceived the counsellor to be ‗truly concerned about their well-being' and ‗understands the stress faced' by the participant. Satisfaction, in this dimension, was further influenced by the provision of having adequate information to make an informed decision about ‗the blood test and surveillance'. Item 3d is in close proximity and suggests that satisfaction with these items was additionally influenced by the perception that the session was the ‗right length of time'. Item 3c (feeling better about health after genetic counselling session), acts as an outlier and does not contribute significantly to satisfaction. There is however no strong association between satisfaction and any of the

demographic variables (characteristics of the study participants), which confirms the findings of De Marco et al (2004).

Referral to predictive testing programme

The large majority of PT participants had been informed about the availability of testing through a family member (93.7%). This occurred via the participants' parent (with LS) in 45.2% (14/31) of cases, by a sibling who had previously had genetic testing in 29.7% (9/31), via a second-degree relative for 16.1% (5/31) and by the parent without the family history of LS for 9.7% (3/31). Only two participants were not informed about PT through a family member and reported direct contact by the GESC as their source of information about the availability of PT.

Period of awareness prior to predictive testing

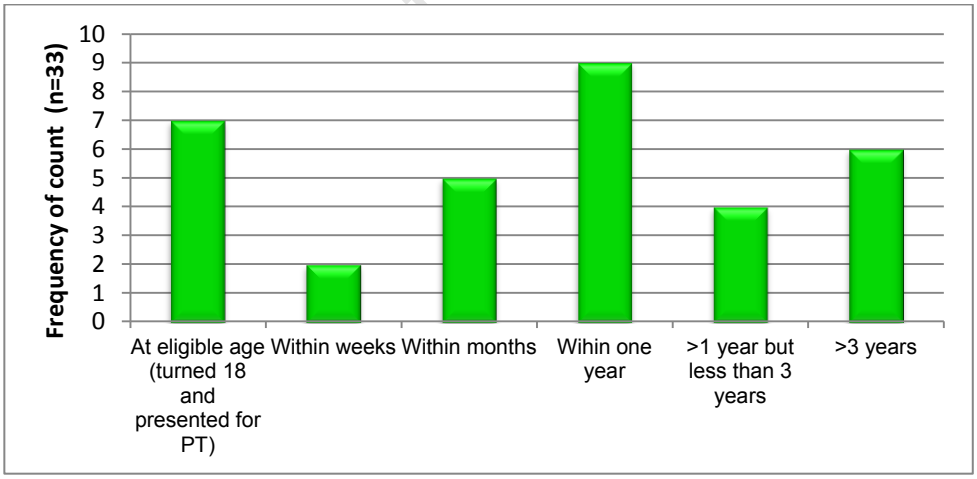

Figure 49: Period of awareness prior to entering into PT.

The mean age of participants presenting for genetic testing within weeks or months (but less than one year) of learning about the PT programme was 28 years and for those participants presenting later than one year 31.8 years (Figure 49). Seven participants (21.7%) presented for testing in the year that they turned 18 years. These individuals had been aware of testing from a

young age and entered into PT upon becoming eligible for testing (18 years of age).

Having observed affected relatives with cancer (living elsewhere), or living with an affected family member, did not typically influence the time period to presenting for PT. However, a trend appeared among those eleven individuals living with an affected family member who had died from CRC. The majority of these individuals illustrated a shorter period to entering into PT (81.8%) suggesting that the exposure of a cancer-related death may act as a facilitator towards earlier genetic testing (Table 80).

Table 80: The influence of the level of exposure to colorectal cancer on the time to presenting for PT (n=26)*.

		Frequency	
Exposure to CRC	Time to presenting for PT	N	Percentage
Affected family members living elsewhere	< One year	4/9	(44.5%)
	> One year	5/9	(55.5%)
Lived with affected family member (with CRC)	< One year	3/6	(50%)
	> One year	3/6	(50%)
Lived with affected family member who died of CRC	< One year	9/11	(81.8%)
	> One year	2/11	(18.2%)

*The seven participants who presented as soon as they became eligible were excluded from the analysis.

Event triggering request for predictive testing

The significant life events triggering the participants to request PT are listed in Table 81.

Table 81: Life event triggering request for PT (n=33).

Trigger event	Frequency	Percentage
Family member recently diagnosed/died of CRC	12/33	36.3%
GESC in town/convenience (near physical location of PT centre)	8/33	24.2%
Major stressful event completed and ready to engage with PT	4/33	12.1%
Request/pressure from family member	3/33	9.1%
Concerning symptoms	2/33	6.1%
Youngest sibling eligible (facilitates group attendance of siblings)	2/33	6.1%
Family member's clinic appointment	2/33	6.1%
Total		100%

Motivation for entering into predictive testing

Although Hadley et al (2003) illustrated that the majority of individuals attending PT believe that the single most important reason for undergoing testing is to learn about the children's risk, this was not the case in the SA cohort. In contrast, it is noteworthy that only 39.8% (13/33) stated that their main motivation for testing included clarifying the risk for their (future) children.

Most participants reported two or three main reasons for engaging in PT. Eighty-four percent (29/33) reported that testing was undertaken to determine if cancer screening was required, 81.7% (27/33) to reduce the level of uncertainty and 69.7% (23/33) to plan for the future. This planning, however, did not seem to take much cognisance of marital planning (15.2%), employment decisions (21.2%) or reproductive decisions (39.8%). Having a family member recommend PT (51.7%) carried greater weighting than that of a doctor's recommendation (24.2%) (Table 82). The findings of the primary motivations for genetic testing in this study are similar to that reported on by Claes et al (2003) and Esplen et al (2001) in individuals undergoing PT for LS and Lerman et al (1996), in individuals considering genetic testing if it become available to them in the future (individuals were FDR of CRC patients without a known mutation).

Table 82: Rating frequencies per item of factors affecting decision to undergo PT (n=33).

	Items	A lot (1)	Moderately (2)	Not at all (3)
4a	Planning for the future	23	5	5
4b	Marital decisions	5	9	19
4c	Reproductive decisions	13	4	16
4d	Clarifying risk for (future) children	13	2	18
4e	Employment decisions	7	7	19
4f	Reducing uncertainty	27	4	2
4g	Doctor recommended it	8	3	22
4h	Self-evident	22	8	3
4i	Family member/partner urged you to go	17	6	10
4j	To find out if surveillance was required	28	4	1

Understanding of predictive testing

According to Doak et al (1998) simply asking a question which requires a yes or no answer does not address understanding or comprehension of the medical information given to patients. To verify that the purpose of PT was understood by the participants, they were required to explain PT in their own words. Education (tertiary education) and ethnicity (White) were associated with a greater understanding of the purpose of PT. Participants who could not correctly explain PT were most often of a lower education background (63.2%) and of Mixed Ancestry (48%) (Table 83). The link between ethnicity and education has been identified in Figure 48 (page 224).

Table 83: Cross-tabulation of the understanding of PT and selected participant characteristics (n=33).

	Purpose of predictive genetic testing (PT)			
	Knows		Does not know	
Gender	11/18 (male) (61.1%)	9/15 (female) (60%)	7/18 (male) (38.9%)	6/15 (female) (40%)
Ethnicity	13/25 (MA) (52%)	7/8 (W) (87.5%)	12/25 (MA) (48%)	1/8 (W) (12.5%)
Tertiary education	12/14 (Yes) (85.7%)	7/19 (No) (36.8%)	2/14 (Yes) (14.3%)	12/19 (No) (63.2%)

Expected emotional outcome subsequent to predictive testing

Following the pre-test genetic counselling session, participants were asked how they would feel if the PT revealed a mutation-positive status. The expected outcomes are shown in Figure 50.

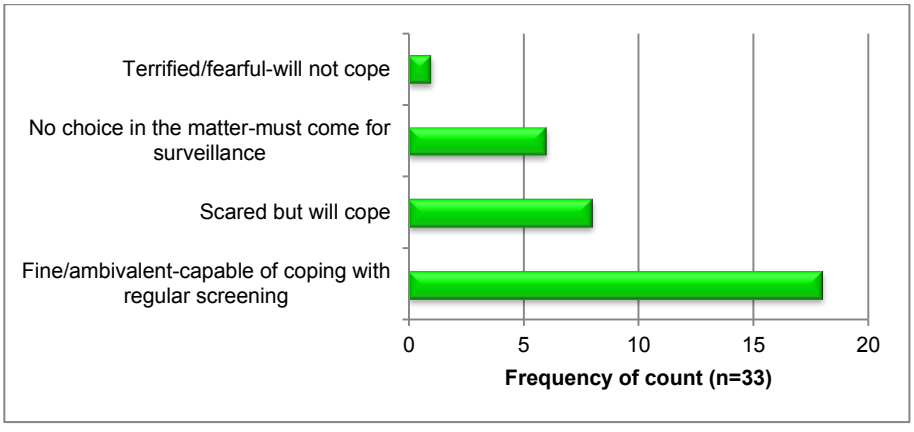

Figure 50: Perceived emotional reactions to outcome of PT.

It is encouraging to know that the majority (54.5%) of participants, embarking on PT, expressed that they would be able to cope with a mutation-positive test result as they were able to deal with regular colonoscopic screening. Eight participants (24.2%) reported that they were scared about surveillance, but would cope with the regular colonoscopies and five (15.2%) explained that they did not want to think about the implications of being mutation-positive, but would definitely attend regular screening if required. Of concern is the one participant who did not perceive herself coping with a positive test result. She was 18 years old, of Mixed Ancestry and had completed secondary schooling. Although her father had developed CRC, she had not lived with him.

Self-perception of result prior to predictive testing

Table 84: The comparison of perceived PT result to actual PT result (n=22).

	Mutation-positive	Mutation-negative	Ambivalent	Total
Perception prior to PT	2/33 (6.1%)	5/33 (15.2%)	26/33 (78.8%)	
PT result	11/22 (50%)	11/22 (50%)	-	
Total	56.1%	65.2%	78.8%	100%

Some percentages may not add up to a 100% as a result of rounding-off.

Seven participants had personal perceptions about their mutation status prior to PT, confirming the findings of other studies where expectations are based on preconceived notions (Esplen et al 2003; Evers-Kiebooms et al 2000; McAllister 2003; Prucka et al 2008; Trepanier et al 2004). For two participants, expectation of a mutation-negative result was based on having a sibling who had not inherited the mutation and feeling healthy at the time of PT. The two participants who perceived themselves to carry a disease-causing mutation based the expectation on the extent of relatives with CRC within the family and having had a sibling die at 16 years from CRC.

4. 14 POST-PREDICTIVE TEST RESULT

Outcome of predictive testing

The number of mutation-positive and mutation-negative results per gender (among those participants who attended their result-giving session) is presented in Table 85. The average age of those participants testing positive was 28.5 years and those with a negative PT result, 30.9 years.

Table 85: PT result per gender of the participants (n=22).

	Attended for PT result (n=22)		
	Mutation - positive	Mutation-negative	Total
Female	4/11 (36.4%)	8/12 (66.7%)	
Male	7/11 (63.6%)	4/12 (33.3%)	
Total			100%

The uptake rate of PT was 100% for this study (all 33 individuals participating in the research study chose to have a genetic test), which greatly exceeds published figures (43-75%) and suggests that participants were eager to accept PT for a treatable disease (Aktan-Collan et al 2000; Codori et al 1999; Hadley et al 2003). However, only 23 participants (69.7%) returned for the test result. Eight participants (24.2%) did not attend their scheduled result-giving session as a result of: waiting for a family member to join; having a family member die of CRC; conflicts with work/studies and transport problems. Two participants (6%) were working in a different province at the time and intended to contact the GESC to schedule an appointment at a more convenient time.

The types of mutations identified in the mutation-positive cohort are displayed in Table 86.

Table 86: Specific Lynch syndrome mutation among mutation-positive cohort (n=11).

Mutation	Frequency	Percentage
MLH1 (Exon 13 c. 1528C>T)	8/11	72.7%
MSH2 (Exon 8 c. 1340-1341insGG; exon13 c. 1459C>T)	3/11	27.3%

The characteristics of those participants not returning for their PT result are shown in Table 87.

Table 87: Characteristics of participants who did not return for their genetic test result (n=10).

Participant	Gender	Age	Ethnic group	Employment status	Education (highest level)	GESC
P4	F	19	MA	Student	Tertiary	Outreach
P5	F	18	W	Unemployed	Secondary	Hospital
P6	M	22	W	Employed	Secondary	Hospital
P13	M	20	MA	Unemployed	Junior	Hospital
P20	M	2	MA	Employed	Tertiary	Outreach
P21	M	25	MA	Employed	Tertiary	Outreach
P22	M	20	MA	Employed	Junior	Outreach
P27	M	40	MA	Employed	Junior	Hospital
P29	M	23	MA	Employed	Tertiary	Hospital
P33	F	61	MA	Employed	Junior	Hospital

Disclosure of predictive test results

There was no specific trend as to who the participants disclosed their genetic test results when comparing the mutation-positive to the mutation-negative cohort. All except one participant had disclosed the mutation status within one month of receiving the PT result. This individual stated that she had not disclosed her result to her family as she could not trust them with the confidentiality of the information (she had tested positive for the familial mutation predisposing to CRC). Eleven participants (47.8%) had disclosed their genetic test result to the immediate family only; eight participants (34.8%), divulged the information to all their family and friends, and three (13%) limited the discussion of their result to their siblings. In all three cases, the parent had not been informed as they had already died of CRC. Disclosure to children, among those participants testing positive, did not occur due to the young age of their offspring (average age 6.3 years) and among the mutation-negative counterparts to avoid undue anxiety and concern.

Satisfaction with process and outcome of predictive testing

Table 88: A subset of categories relating to satisfaction with the PT process (n=22).

Item	Description	Agree	Disagree
E2	Satisfied with decision (undertaking PT)	22/22 (100%)	0/22 (0%)
E3	Trusting of test result	20/22 (91%)	2/22 (9%)
E6	Eligibility age (18 years)	17/22 (77.3%)	5/22 (22.7%)
E7	Pre-test counselling and testing on same day	21/22 (95.5%)	1/22 (4.5%)
E8	Satisfaction with the amount of time taken to receive PT result	15/22 (68.2%)	7/22 (31.8%)

Both the mutation-positive and mutation-negative individuals were satisfied with their decision to take the PT (100%) and regret of being tested was not expressed by any of the participants. However, two participants did not fully trust the test result. One participant received a mutation-positive result where some of his personal details were incorrect and the other participant who had been given a mutation-negative result expressed that he would always be concerned as he had expected to carry the disease-causing mutation. These two participants were both male and highly educated.

All participants (100%) would recommend PT and genetic counselling to their family members, mostly to ‗obtain information on their health', to ‗know their status and attend for surveillance only if necessary' and to decrease uncertainty: ‗better to know than to worry about something you don't know about'. This is much higher than the figure of 75% reported by Stadler and Mulvihill (1998).

The majority (95.5%) of participants were satisfied with a single pre-test genetic counselling session, which is in conformity with previous reports highlighting a preference for a shortened PT and counselling protocol among individuals with LS (Aktan–Collan et al 2000; Brain et al 2005; Collins et al 2007; Esplen et al 2001; Lerman et al 1996; Meiser et al 2004).

Over a third (7/22) of individuals undergoing PT were dissatisfied with the amount of time taken to receive their test results. These rates are comparable to Bleiker et al (1997), who found that 37% of their sample receiving genetic counselling for familial cancer were dissatisfied with the length of time that they had to wait for their test result. The average time from pre-test counselling to the time that the participant was notified that their PT result was available, was 5.8 months. The average time from testing to result disclosure was 5.2 months and 10 months, for the WC cohort and NC cohort, respectively. Factors influencing the length of time taken to receive the test result were: availability of an appointment with the genetic counsellor at GSH, field trips to the NC (beyond that of the scheduled outreach trip), ability to travel to GSH to receive results at the hospital sector of GESC (instead of the outreach GESC).

Emotional outcome following predictive test disclosure

Thoughts about the PT result, during the waiting period, occurred _almost all the time' for three participants (15%), _a lot' for five participants (25%), _every now and then' for the majority (50%) and _not at all' for two participants (10%). Five of the eight participants who reported thoughts about the PT result to occur _a lot' or _almost all the time' were male. The mean age of these participants were typically older than the average age of the entire group (36.6 years versus 28.7 years). The emotional reaction to receiving either a mutation-positive of mutation-negative PT result is described in Table 89. As would be expected, the majority of participants testing mutation-negative, reported feeling incredibly lucky, happy or relieved by the news while those testing positive were shocked, saddened or anxious. Overlapping categories between both groups included, _unexpected result due to a preconceived notion' and _confirmed belief of expected result'.

Table 89: Emotional reaction following predictive test result disclosure (n=22).

Category	Frequency among mutation-negative cohort	Excerpts relating to category definition	Frequency among mutation-positive cohort	Excerpts relating to category definition
Very happy, incredibly thankful, relived	8/12	"So relieved, it was like this massive burden had been taken off my shoulders, I had this constant worry and now… to have gotten rid of it…" (female, 18 years). "Just so incredibly relieved!" (female, 18 years).		
Unexpected result due to preconceived notion	3/12	"Can I tell you that I almost fell off my chair when I heard… [laughs], I had prepared myself for bad news and had really believed I would carry the gene, it was so unexpected to hear that I did not, I still pinch myself to make sure that I am not dreaming/…/" (male, 45 years). "Terrified with fear, I had prepared for a positive result and was absolutely shocked that it was negative, when [X] died (brother who developed CRC at 16 years) I went for the test but I was just too scared to go through with it, I knew I would get told that I had the same as [X], so I just couldn't and then when I had it done, I was ready for the news and then, then it was negative…(translated, female, 19 years).	2/10	"Well, actually in all honesty I was a little shocked, and surprised, I thought the gene was connected to the other side of the family, the [X] side, you see my cousin went for this test and he was negative and the family history is so much stronger on his side than mine, and he is closer, you know more connected to the [X] side of the family, I am only half [X], so I did not really expect it. When I heard I cancelled my holiday, you kind of want to be around the comfort and safety of the known when you hear something like this" (male, 38 years). "I must admit, I was a little shocked by the news - my two brothers were free of this thing and I guess I thought that I would also be, I will be okay, but it is just that that bit of hope has been taken away, now I must deal with this thing…" (male, 18 years).
Confirmed believe of perceived/ expected result	1/12	"I had this feeling that I would be negative, I do not know why, just this gut feeling, so the result just confirmed that for me" (translated, female, 21 years).	1/10	"I was not really surprised, you see most of my family have it, so I was very likely to also have it" (translated, female, 31 years).
Shocked, nervous, very upset			7/10	"Nervous but I am very positive, if something is wrong I want to find out so that I can fix it and this result allows me that ability" (female, 32 years). "…did not expect it to be positive so it was hard to deal with that…with the news, quite devastating and really gets you down…" (translated, male, 38 years). "../ I really did not think I would be positive, I was quite shocked by the result" (translated, male 18 years). "I was so incredibly upset, but I believe every thing happens for a reason, so…there must be some explanation, some good that will come from this one day" (translated, female, 19 years).

Psychological impact of predictive genetic testing

Hopwood (1997) suggested that a negative psychological outcome, subsequent to PT, can be minimised if testing is provided in combination with genetic counselling, support and appropriate follow-up. Research has shown that individuals undergoing PT for LS do not demonstrate excessive levels of anxiety and depression, with the exception of a short-term increase in individuals testing positive (Akan-Collan et al 2001; Bleiker et al 2003; Claes et al 2005).

Figure 51 depicts the mean scores on the DUKE-AD scale at pre- and post-testing time periods by the mutation status of the individual. Mutation-positive participants illustrated slightly elevated mean scores immediately after receiving the PT result, when compared to their mutation-negative counterparts (5.0, SD=2.8 versus 4.9, SD=2.9). While mutation-positive participants demonstrated higher mean values post-test than the mutation-negative cohort, both groups could be seen to demonstrate decreased levels of anxiety and depression (as measured by DUKE-AD score) one month post result delivery. These findings are congruent with other studies, conducted in developed countries, which illustrate similar trends for individuals undergoing PT (Aktan-Collan et al 2001; Bleiker et al 2003; Claes et al 2004; Esplen et al 2001; Meiser et al 2004; Shiloh et al 2008; Van Oostrom et al 2007).

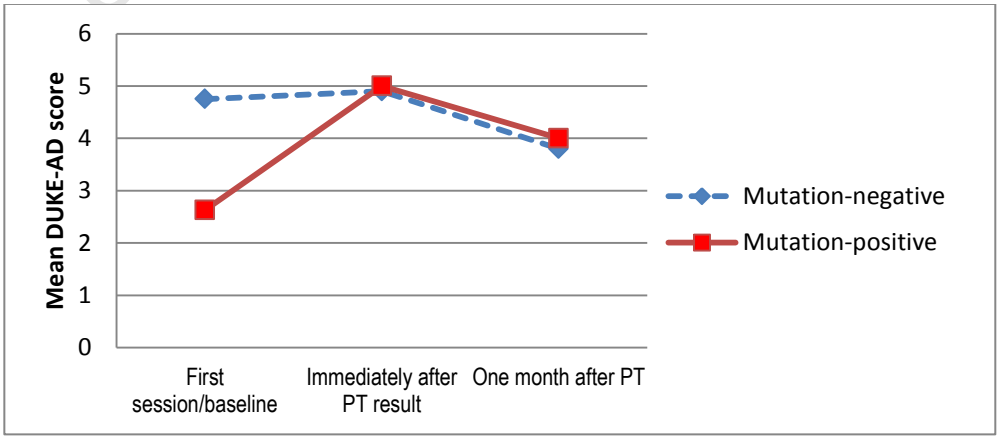

Figure 51: Comparison of mean DUKE-AD score for mutation-positive and mutation-negative participants at assessment time points before and after disclosure of PT results.

Mean cancer worry scores displayed an increasing effect from pre-test to the time period ‗immediately after the disclosure of PT result' but decreased means appeared after one month for both groups (Figure 52). Of interest is that the mean score at this time point, for the mutation-negative cohort, was higher than the mutation-positive group (8.4, SD=2.5 versus 7.0, SD=2.9), which is in contrast to expected results. However the measure illustrated a higher baseline score among those mutation-negative individuals (7.6, SD=2.2 versus 6.9, SD=2.2) following the pre-test genetic counselling session. This group of mutation-negative individuals also reported higher baseline scores on the DUKE-AD measure (Figure 51). Encouragingly, however, the mutation-negative individuals reported a score below their baseline value as well as that of the mutation-positive cohort at the time point of month preceding the delivery of their test result.

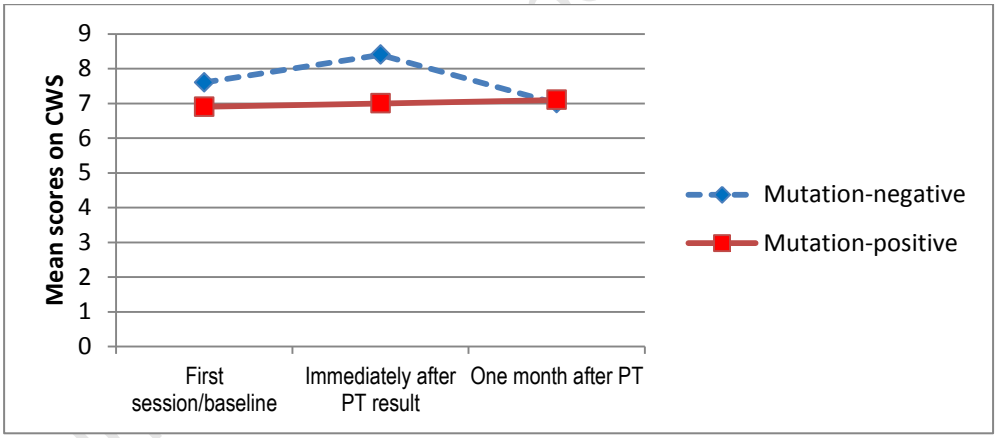

Figure 52: Comparison of mean scores of cancer-related worry for mutation-positive and mutation-negative participants at assessment time points before and after disclosure of PT results.

The fluctuating pattern observed in cancer worry scores (from baseline to immediately after PT result), is in contrast to other studies, where cancer worry has been shown to remain high for mutation-positive individuals and decrease for mutation-negative individuals (Gritz et al 2005). Negative results are not always associated with stress reduction (Evans 2006). Individuals, who receive a mutation-negative result may still continue to worry about their cancer-related risk if they have difficulty integrating this new knowledge with the cancer history in their family:

> „I do not have one word for how I felt that day, if I had to explain the impact of the news…I guess I would have to say surprised, relieved, no, more like a sense of the news that I received was unexpected. I really believed I was going to be positive /…/ the chances were against me - my sister had it and she was the oldest and my brother did not have it, he was the middle child, then I should have it as I am the youngest…also I look like my dad, we have the same features and that together with me being the youngest, the third child, where one had it one did not have it and then me, I should have it, if you look at that pattern. So I guess I should be relieved but I still worry, as everything was pointing to me having it, the gene…" (male, 23 years).

Furthermore, adverse sequelae after obtaining a mutation-negative result may relate to ‚survivor guilt', disbelief in test result, repercussions of family relationships or regret over life decisions made prior to testing based on ‚believed susceptibility' (Hopwood 1997; Baker et al 1998, Harper 1998; Weil 2000). Notably, the CWS scores were quite comparable between the mutation-positive and mutation-negative cohort when the scale was completed for the third time (one month preceding PT result delivery) (7.1, SD=2.4 versus 7.0, SD=2.9). Mutation-positive individuals may experience relief from uncertainty and appreciate the benefits of regular surveillance even if found to carry the predisposing mutation. Of interest is that six of the 11 participants who tested positive had already undergone colonoscopic screening prior to the last interview (one month preceding PT result delivery), when the CWS was completed for the third time. The trend in these results are similar to that of the findings of Hadley et al (2011) who identified that mutation-positive individuals, receiveing a colonoscopy within six months of their PT result being disclosed, reported less depressive symptoms than those carriers who did not undergo a colonoscopy within this time period.

A GLM (general linear model) multivariate repeated measure procedure was used to analyse anxiety and depression, as measured by the DUKE-AD Scale, and cancer worry, as measured by the CWS, of the 33 participants receiving either a mutation-positive or mutation-negative PT result. Responses to the scale items at the three time periods were treated as ‚within variables'. The mutation status (either mutation-positive or negative) was treated as ‚between variable'.

A multivariate analysis, considering the average DUKE-AD scores at the three assessment time points and the mutation status, showed no significant effects.

Table 90: Multivariate tests at assessment time points on the DUKE-AD scale before and after disclosure of PT results including the effect on mutation status.

Multivariate Tests[c]							
Effect		Value	F	Hyp df	Error df	Sig.	Power[b]
DUKE-AD	Pillai's Trace	0.255	3.428[a]	2	20	0.052	0.576
	Wilks' Lambda	0.745	3.428[a]	2	20	0.052	0.576
	Hotelling's Trace	0.343	3.428[a]	2	20	0.052	0.576
	Roy's Largest Root	0.343	3.428[a]	2	20	0.052	0.576
DUKE-AD* Mutation status	Pillai's Trace	0.176	2.137[a]	2	20	0.144	0.386
	Wilks' Lambda	0.824	2.137[a]	2	20	0.144	0.386
	Hotelling's Trace	0.214	2.137[a]	2	20	0.144	0.386
	Roy's Largest Root	0.214	2.137[a]	2	20	0.144	0.386

[a]Exact statistic.
[b]Computed using alpha = 0.05.
[c]Design: Intercept + mutation status within subjects design: DUKE-AD.

Table 91 reveals that the changes measured by the DUKE-AD scale over time (repeated levels of the within factor) were not significant. The interaction between being mutation-positive or mutation-negative and anxiety and depression, as measured by the DUKE-AD scale, was not present. This is shown in Figure 53 (page 240).

Table 91: Tests of within-subject effects.

		Type III SS	df	MS	F	Sig.	Power[a]
DUKE-AD	Sphericity Assumed	0.217	2	0.108	0.998	0.377	0.212
	Greenhouse-Geisser	0.217	1.846	0.118	0.998	0.372	0.204
	Huynh-Feldt	0.217	2.000	0.108	0.998	0.377	0.212
	Lower-bound	0.217	1.000	0.217	0.998	0.329	0.159
DUKE-AD * Mutation	Sphericity Assumed	0.565	2	0.282	2.598	0.086	0.490
	Greenhouse-Geisser	0.565	1.846	0.306	2.598	0.091	0.468
	Huynh-Feldt	0.565	2.000	0.282	2.598	0.086	0.490
	Lower-bound	0.565	1.000	0.565	2.598	0.122	0.337
Error (DUKE-AD)	Sphericity Assumed	4.566	42	0.109			
	Greenhouse-Geisser	4.566	38.774	0.118			
	Huynh-Feldt	4.566	42.000	0.109			
	Lower-bound	4.566	21.000	0.217			

[a]Computed using alpha = 0.05.

Table 92 shows that the difference between those participants testing mutation-positive and those with a mutation-negative result and with DUKE-AD reponses, as a dependent variable, are not significant.

Table 92: Tests of between-subject effects.

Transformed Variable: Average						
Source	Type III Sum of Squares	Df	Mean Square	F	Sig.	Observed Power[a]
Intercept	135.033	1	135.033	278.437	0.000	278.437
Mutation	1.120	1	1.120	2.309	0.144	2.309
Error	10.184	21	0.485			

[a]Computed using alpha = 0.05.

Table 93 shows that the estimated marginal means over time were not significant.

Table 93: The relationship between DUKE-AD score and mutation status over assessment time points.

Mutation status	DUKE-AD	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Mutation-positive (carrier)	Baseline	1.091	0.129	0.823	1.359
	PT result session	1.364	0.154	1.044	1.683
	One month	1.364	0.154	1.044	1.683
Mutation-negative (non-carrier)	Baseline	1.583	0.123	1.327	1.840
	PT result session	1.583	0.147	1.277	1.890
	One month	1.417	0.147	1.110	1.723

A graphical representation of the marginal means appears in Figure 53.

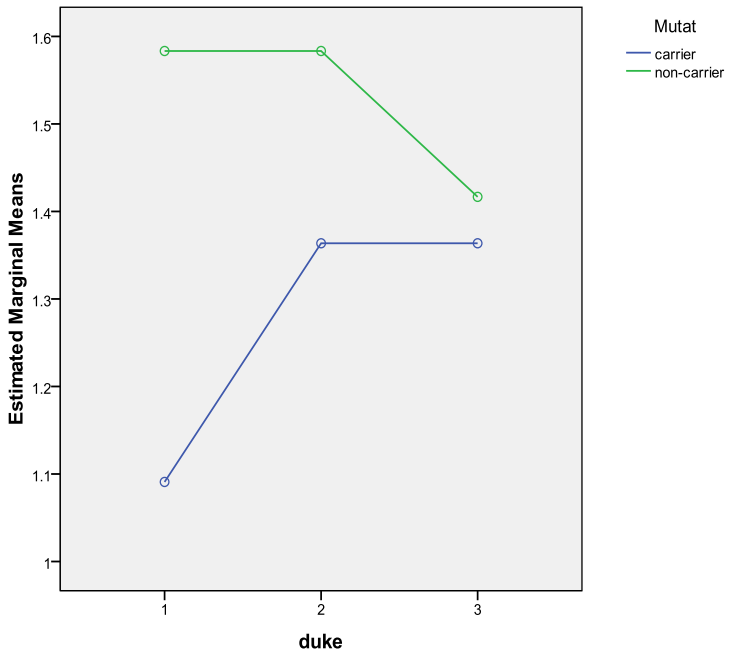

Figure 53: Marginal means of the DUKE-AD measure per mutation status.

No multivariate effects of repeated measures as measured by the DUKE-AD scale and mutation status were found when the DUKE-AD key (Table 63, page 198) was applied (Table 94).

Table 94: The relationship between CWS score and mutation status when DUKE-AD key is applied.

Mutation	DUKE-AD	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Mutation-positive	1	1.091	0.129	0.823	1.359
	2	1.364	0.154	1.044	1.683
	3	1.364	0.154	1.044	1.683
Mutation-negative	1	1.583	0.123	1.327	1.840
	2	1.583	0.147	1.277	1.890
	3	1.417	0.147	1.110	1.723

The same procedure was applied to analyse the CWS of the 33 participants that received either a mutation-positive or negative test result.

Table 95: Multivariate tests at assessment time points on CWS before and after disclosure of PT results including effect on mutation status.

Multivariate Tests[c]							
Effect		Value	F	Hyp df	Error df	Sig.	Observed Power[b]
CWS	Pillai's Trace	0.074	0.802[a]	2	20	0.462	0.167
	Wilks' Lambda	0.926	0.802[a]	2	20	0.462	0.167
	Hotelling's Trace	0.080	0.802[a]	2	20	0.462	0.167
	Roy's Largest Root	0.080	0.802[a]	2	20	0.462	0.167
CWS* Mutation	Pillai's Trace	0.071	0.769[a]	2	20	0.477	0.162
	Wilks' Lambda	0.929	0.769[a]	2	20	0.477	0.162
	Hotelling's Trace	0.077	0.769[a]	2	20	0.477	0.162
	Roy's Largest Root	0.077	0.769[a]	2	20	0.477	0.162

[a]Exact statistic.
[b]Computed using alpha = 0.05.
[c]Design: Intercept + mutation status within subjects design: CWS.

The Mauchly's test of sphericity tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix (Table 96).

Table 96: Mauchly's test of sphericity (tests of within-subjects affects).

Mauchly's Test of Sphericity[b]							
Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
CWS	0.717	6. 654	2	0.036	0.779	0.871	0.500

[a]May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the tests of within-subjects effects (Table 97).
[b]Design: Intercept + mutation within subjects design: CWS.

Table 97 shows that no significant effects, over time, were found (sphericity ignored).

Table 97: Tests of within-subject effects.

Source		Type III SS	df	MS	F	Sig.	Power[a]
CWS	Sphericity Assumed	4.799	2	2.399	0.412	0.665	0.112
	Greenhouse-Geisser	4.799	1.559	3.078	0.412	0.616	0.105
	Huynh-Feldt	4.799	1.741	2.756	0.412	0.638	0.108
	Lower-bound	4.799	1.000	4.799	0.412	0.528	0.094
CWS * Mutation	Sphericity Assumed	5.900	2	2.950	0.506	0.607	0.128
	Greenhouse-Geisser	5.900	1.559	3.785	0.506	0.562	0.118
	Huynh-Feldt	5.900	1.741	3.388	0.506	0.582	0.122
	Lower-bound	5.900	1.000	5.900	0.506	0.485	0.104
Error (CWS)	Sphericity Assumed	244.854	42	5.830			
	Greenhouse-Geisser	244.854	32.735	7.480			
	Huynh-Feldt	244.854	36.567	6.696			
	Lower-bound	244.854	21.000	11.660			

[a]Computed using alpha = 0.05.

Table 98 shows that the difference between those participants testing mutation-positive and those with a mutation-negative result and with CWS responses as a dependant variable is not significant.

Table 98: Tests of between-subject effects.

Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Observed Power[a]
Intercept	1254.184	1	1254.184	472.849	0.000	1.000
Mutation	2.512	1	2.512	0.947	0.342	0.153
Error	55.700	21	2.652			

[a]Computed using alpha = 0.05.

Table 99 shows that the estimated marginal means did not illustrate any significant effects over time.

Table 99: The relationship between CWS score and mutation status over assessment time points.

Mutation	CWS	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Mutation-positive (carrier)	Baseline	6.909	0.670	5.517	8.302
	PT result session	7.091	0.821	5.383	8.799
	One month	7.182	0.813	5.492	8.872
Mutation-negative (non-carrier)	Baseline	7.667	0.641	6.333	9.000
	PT result session	8.417	0.786	6.781	10.052
	One month	7.083	0.778	5.465	8.701

Figure 54 illustrates a graphical representation of the means per the mutation status.

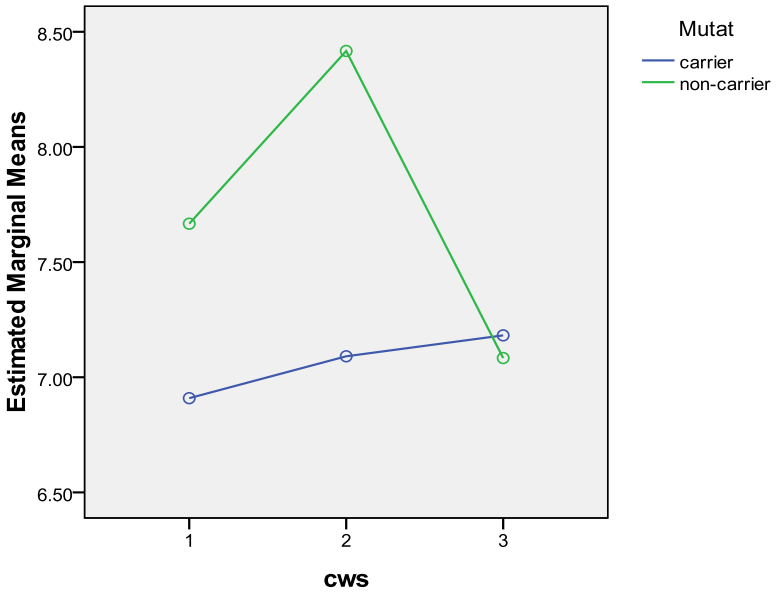

Figure 54: Marginal means of the CWS measure per mutation status.

4. 15 SUMMARY OF RESULTS/FINDINGS FOR GROUP B

Satisfaction with genetic counselling was high among the participants in Group B (80.3%). The information received during the pre-test counselling session, found to be the most valued by the participants, related to the cause, symptoms, testing and treatment of LS. Satisfaction with genetic counselling was not correlated with any demographic variables. However, satisfaction may have been uniformly high due to counselling and genetic testing being offered free of charge.

The large majority of participants entered into PT to determine if cancer surveillance was required (81.7%). Participants were mostly informed about the availability of the genetic test through a family member (93.7%). Of concern is that 39.4% of participants could not explain the purpose of PT,

even after receiving extensive pre-test counselling. These individuals were mostly from a lower education background and of Mixed Ancestry. The uptake rate of PT was however not influenced by this and remained high, with 100% of participants accepting PT (although only 69.7% returned for their test result). Seventy percent of individuals presented for PT within a year of learning about the availability of the genetic test and having a family member die of CRC acted as a facilitator to entering into PT, within a shorter time frame.

The emotional outcome, following the delivery of the PT result, identified that expectations reflected personal views on family history, coping mechanisms and having a _gut feeling'. Receiving either a mutation-positive or mutation-negative test result did not typically influence disclosure rates nor did it illustrate any trends as to who the participants disclosed their mutation status.

The psychological impact of embarking on a process of PT was investigated for the first time in SA cohort. Mean DUKE-AD scores, among both the mutation-positive and mutation-negative participants, were congruent with reported trends for individuals undergoing PT (mutation-positive participants demonstrated higher scores than the mutation-negative cohort). However mean CWS scores were unexpectedly higher among mutation-negative individuals when compared to the mutation-positive cohort. The results are somewhat unexpected and warrant further investigation with larger sample sizes.

The conclusion of the study is presented in the following Chapter.

CHAPTER FIVE: CONCLUSION

CHAPTER FIVE

CONCLUSION

5.1 CONCLUSION

The main aims of this study were firstly, to appraise the GESC from the perspective of the users to ascertain the experiences and level of satisfaction with the programme; secondly, to measure the level of adherence to recommended screening guidelines and to determine the impact of socio-economic status, education, physical barriers and psychosocial factors on adherence; and thirdly to determine the uptake rate of PT and to identify and explore the referral pathways and communication networks leading to the GESC.

Two domains anchor the GESC, the PT programme and the endoscopic surveillance service. This was the first time that research has been conducted to appraise the GESC. The data, with reference to each of the dimensions differ somewhat to that of the international literature. In many cases the discrepancy between the previously published findings and this study can be attributed to the socio-economic context of the participants, highlighting that findings from a specific population group do not illustrate generalisability. Furthermore, results unique to the GESC may not necessarily apply to other established cancer genetic programmes in other parts of the country or developed countries.

5.1.1 GENETIC AND ENDOSCOPIC SURVEILLANCE PROGRAMME (GROUP A)

The majority of participants (90.2%) evaluated the service offered by the GESC as satisfactory. The participants‘ level of knowledge of LS, however, was poor, particularly with regard to inheritance and CRC risk. The only factor

affecting knowledge was that of ‗length of time in the GESC', whereby participants who had been in the programme for a longer period of time had a greater level of knowledge. This suggests that repetition of information facilitates consolidation of concepts and understanding of the message received during counselling, particularly in a group of individuals with a low education level.

The ‗length of transport time to GESC' and use of ‗free ambulance service' was found to be over-represented in non-adherent participants. In addition women over the age of 50 years were more likely to miss their colonoscopic appointment. Furthermore, the concept that screening was required prior to the presentation of concerning bowel symptoms, even if the participant felt ‗healthy/fine', was not recognised among 56% of participants.

There was a large discrepancy between self-report and actual adherence to recommended screening guidelines and basing adherence rates on self-reported screening attendance led to an over-estimation of compliance. Understanding the actual screening process, as experienced by the participants, can aid the understanding of fear or undesirable outcomes and offer counselling opportunities to prevent or circumvent them. In other words, participants with positive experiences are more likely to be compliant with screening guidelines underscoring the necessity to try and deal with any unpleasant outcomes.

Colon preparation was recognised as the most difficult part of surveillance and simply changing the type of preparation mixture, to that of the participant's preference, could facilitate a more positive preparatory experience. Less than a third of participants found the colonoscopy painful and the pain/discomfort associated with the procedure was recognised to decrease over time.

The facilitators to adherence were typically similar to those previously identified in the literature, namely to ‗maintain helath' and to ‗avoid cancer-related suffering'. The barriers pertained mostly to colon preparation and transport concerns and additional barriers, unique to the GESC were identified (for example All-Pay). The only demographic factor to illustrate an effect on adherence was the age of the participant. Older participants were less adherent.

Participants reported high disclosure rates pertaining to their genetic test results and typically divulged the information within 24 hours of receiving the result. However, the direct implications to other family members were relayed less often in conversation, especially in the case of children and second-degree relatives. The calculated uptake rate of PT among siblings and children of the participants was high (97% and 73.6%, respectively).

The levels of anxiety and depression of the mutation-positive participants were significantly higher than those reported in studies conducted in developed countries. On analysis of the CWS, participants differentiated into those who were less severely plagued by cancer thoughts and worries and those who were more severely affected by having these thoughts affect their mood and behaviour. Under-exposure rather than over-exposure to the familial cancer was found to be a potentially important predictor of distress in individuals with LS.

5.1.2 PREDICTIVE GENETIC TESTING PROGRAMME (GROUP B)

The vast majority of participants entering into PT judged the genetic counselling aspect of the programme as highly satisfactory (80.3%) and 95.5% of participants were happy with a single pre-test counselling session. Aspects of the programme illustrating some dissatisfaction included the time taken to receive the PT result and concerns around the accuracy of the test result.

The majority of participants had been referred to the GESC by a family member and engaged in PT due to one of three main reasons: to determine the necessity of screening, reducing uncertainty and planning for the future.

The uptake rate of PT was high with 100% of participants accepting PT. Receiving a mutation-positive test result evoked expected responses such as shock, anxiety and sadness while those receiving a mutation-negative result were mostly happy or relieved. Regret of being tested for the familial susceptibility was not expressed by any of the participants and all participants would recommend testing to their family members.

The DUKE-AD scores were comparable to the trends identified in the literature, however the CWS scores were higher in participants with a mutation-negative test result when compared to those receiving a mutation-positive result, although this value did decline one month post result delivery, to levels lower than the mutation-positive cohort.

Apects arising from this study of the GESC which need to be addressed in order to improve the processes from the participants‘ perspective are presented in the next chapter.

CHAPTER SIX: RECOMMENDATIONS

CHAPTER SIX

RECOMMENDATIONS

6.1 RECOMMENDATIONS

Following the analysis of the data, the recommendations made by the participants within Group A and Group B as well as those identified by the researcher were discussed with the genetic and clinical team. It was deemed particularly important to address the barriers to the GESC and implement changes, where possible, as soon as they were identified due to the potential effect on cancer-related morbidity and mortality. The majority of suggestions, to improve the service offered by the GESC, have been approved and implemented as indicated below.

6.1.1 RECOMMENDATIONS FROM THE PARTICIPANTS ATTENDING FOR SURVEILLANCE AT THE GESC (GROUP A):

- **Provision of written information on LS, available in Afrikaans with reading levels directed at the literacy level of the participants**. Specific information, as requested by the participants, has been included in the booklet. This pertained to: the cause of cancer (polyp development); concerning bowel symptoms; inheritance and contact details. The booklet has been completed and is in the process of being reviewed with the families attending the hospital GESC and will be discussed with the families attending the outreach GESC in August (during the 2011 outreach trip). This will enable the researcher to determine if the information is written at the appropriate literacy level.
- **Discussion with the ambulance drivers about the need for regular stops to allow for toilet breaks during the journey to the**

GESC has taken place. Feedback has been sought from individuals using the service and if any concerns are reported, supervisors are informed about reckless driving.

- **Clinic appointments made on the same day as family members attending the GESC (unless requested to avoid contact with known relatives).** The participants suggested that having all the family around them offered additional support, a distraction while waiting for the colonoscopy and the group attendance acted as a motivating factor when utilising screening services.
- **Report back on trial results following research enrollment**. Participants have suggested that any new study, within which they may be involved, should provide them with regular updates and feedback should occur in an ongoing manner.

6.1.2 RECOMMENDATIONS FROM THE PARTICIPANTS ATTENDING FOR GENETIC COUNSELLING AND PT (GROUP B):

- **Telephonic contact if results are to take longer than six weeks**. Weekly feedback thereafter with updates on expected time of release of genetic test result to any individual entering into the PT programme.
- **Amend PT protocol to exclude post-test confirmatory bloods.** Participants feel that this supplementary blood sample raises concerns about the accuracy of the result and acts as an additional painful procedure to endure after receiving the PT result, especially in the case of a positive test result. A complete analysis of all PT results since October 1996 to August 2011 was conducted. Concordance between the initial test result and that of the confirmatory post-test result was determined and the confirmatory sample has now been discontinued.

- **More information and details on the colonoscopic procedure preceding the first colonoscopy**. The PT programme now includes a pre-colonoscopic counselling session prior to the first endoscopic procedure. This also offers time to discuss the preparatory experience and to determine if any changes can be made to alleviate problems arising from colon preparation. In addition, individuals attending the GESC have access to genetic counselling at each follow-up surveillance session to clarify any misunderstandings, repetition of the information, consolidation of their knowledge of LS and to discuss recruitment of family members and address any difficulties encountered. As substantiated during this research, knowledge can also be seen to increase with the number of years spent at the GESC and promotes greater recall and understanding of LS-associated information.

6.1.3 RECOMMENDATIONS IDENTIFIED THROUGH THE STUDY:

- **The option of colon preparation at the GESC**. If the available amenities or lack thereof make the preparation process difficult to complete at the individual‘s home, preparation is offered at the GESC. Extra enemas are now kept at the GESC to aid with rapid colon preparation, if required. As far as possible the preferred preparation mixture is to be provided to individuals attending for screening.
- **The most skilled operator is to complete the first colonoscopy**. This ensures that the initial procedure occurs with the least amount of pain. A good experience would be more likely to promote regular attendance and less anxiety and fear associated with the procedure.
- **Date of annual outreach GESC changed**. The date of the outreach clinic has been changed so that it does not co-incide with the date of the government grant payout.

- **Telephonic contact reminder**. A phone call to the individual, a week prior to the GESC appointment, as a reminder of the date of screening.
- **Standard letters for family recruitment.** The letters are also available in Afrikaans and are kept on hand at the GESC to be able to distribute to relatives. The document explains the inherited risk, option of PT and provides the contact details of GESC (Appendix 7).
- **Standard letters for leave of absence.** Standard letters on official headed paper to be available for individuals to present to their employers with regards to the need for annual attendance at the GESC and two day leave of absence for the preparation and procedure (Appendix 8).
- **Greater time devoted to explaining purpose of PT.** Most of the individuals from a lower education background and of Mixed Ancestry (in this study) struggled to understand the purpose of PT. Additional time and possibly a more basic explanation of PT should occur during the counselling session, particularly when individuals from this background are seen.
- **Emphasis on the benefits and necessities of regular screening among the older population.** The higher age groups typically illustrated greater non-adherence and the concept that screening is required even if the individual feels ‗healthy/fine' and prior to the presentation of concerning bowel symptoms, needs to be emphasised.
- **Identification of vulnerable individuals requiring greater emotional support and further psychological counselling.** Vulnerable individuals include those participants with a parental cancer diagnosed during their childhood. Cancer worry is also greater in individuals with less exposure to the effects of the condition within their family. Individuals should complete a DUKE-AD form at each post-test session, and if found to be depressed, referred for further psychological counselling.

- **Approach females and individuals affected with CRC to increase the awareness of PT (and possible uptake of PT) among at-risk family members.** These individuals should be targeted as they are more likely to discuss the option and benefits of PT with the at-risk family members.
- **Adherence studies should include adherence rates obtained from database/medical records.** Research aimed at calculating adherence should capture data from database/medical records to avoid over-estimation of screening attendance as obtained from self-reported adherence rates.
- **An Afrikaans version of the DUKE-AD scale should be compiled.** The DUKE-AD scale should be translated into Afrikaans and validated in collaboration with the authors (Pakerson and Broadhead 1997) who developed it.
- **Re-evaluation of the surveillance and PT programme**. A re-evaluation should be conducted after a period of one year following the recommendations being implemented. Changes in attendance should be re-calculated to determine the effect of implemented changes on compliance.
- **The DUKE-AD and CWS measures should be conducted with a larger sample size**. A greater number of individuals entering into PT for LS should be investigated to allow for further definition of distress and cancer worry among the SA cohort. It would also be beneficial to evaluate the effect of PT in a long-term manner, such as at a yearly follow-up period.
- **The reasons for the delay or late uptake of PT should be investigated.** The mean age of entry into PT was 28.7 years among participants entering into PT in this study. As surveillance is usually initiated once an individual receives a mutation-positive test result, the time period from 18 years until 28.7 years is occurring without colonoscopic screening for many participants. Although LS is typically a late-onset predisposition to cancer and the average age

of cancer diagnosis was 41.5 years in this study, one individual developed CRC prior to this age (Table 14, page 134).

REFERENCES

Aaltonen, L. A., Peltomaki, P., Mecklin, J. P., Järvinen, H., Jass, J. R., Green, J. S., et al. (1994). Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients. *Cancer Research, 54*(7), 1645-1648.

Aaltonen, L. A., Salovaara, R., Kristo, P., Canzian, F., Hemminki, A., Peltomaki, P., et al. (1998). Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *The New England Journal of Medicine, 338*(21), 1481-1487.

Aarnio, M., Mecklin, J. P., Aaltonen, L. A., Nystrom-Lahti, M., & Jarvinen, H. J. (1995). Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. *International Journal of Cancer, 64*(6), 430-433.

Aarnio, M., Salovaara, R., Aaltonen, L. A., Mecklin, J. P., & Jarvinen, H. J. (1997). Features of gastric cancer in hereditary non-polyposis colorectal cancer syndrome. *International Journal of Cancer, 74*(5), 551-555.

Aarnio, M., Sankila, R., Pukkala, E., Salovaara, R., Aaltonen, L. A., de la Chapelle, A., et al. (1999). Cancer risk in mutation carriers of DNA-mismatch-repair genes. *International Journal of Cancer, 81*(2), 214-218.

Abdel-Rahman, W. M., Mecklin, J. P., & Peltomaki, P. (2006). The genetics of HNPCC: Application to diagnosis and screening. *Critical Reviews in oncology/hematology, 58*(3), 208-220.

Abusamra, H., Maximova, S., Bar-Meir, S., Krispin, M., & Rotmensch, H. H. (1987). Cancer family syndrome of lynch. *The American Journal of Medicine, 83*(5), 981-983.

Adhikari, M. (2005). *Not white enough, not black enough. Racial identity in the South African Coloured community*. Cape Town: Double Storey books.

Aktan-Collan, K., Haukkala, A., Mecklin, J. P., Uutela, A., & Kaariainen, H. (2001). Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): A prospective follow-up study. *International Journal of Cancer, 93*(4), 608-611.

Aktan-Collan, K., Haukkala, A., Pylvanainen, K., Jarvinen, H. J., Aaltonen, L. A., Peltomaki, P., et al. (2007). Direct contact in inviting high-risk members of hereditary colon cancer families to genetic counselling and DNA testing. *Journal of Medical Genetics, 44*(11), 732-738.

Aktan-Collan, K., Mecklin, J. P., Jarvinen, H., Nystrom-Lahti, M., Peltomaki, P., Soderling, I., et al. (2000). Predictive genetic testing for hereditary non-polyposis colorectal cancer: Uptake and long-term satisfaction. *International Journal of Cancer, 89*(1), 44-50.

Aktan-Collan, K. I., Kaariainen, H. A., Kolttola, E. M., Pylvanainen, K., Jarvinen, H. J., Haukkala, A. H., et al. (2011). Sharing genetic risk with next generation: Mutation-positive parents' communication with their offspring in lynch syndrome. *Familial Cancer, 10*(1), 43-50.

American Society of Human Genetics ad Hoc Committee on Genetic Counseling. (1975). Genetic counseling*. American Journal of Human Genetics*, 27: 240-242

American Society of Human Genetics Social Issues Subcommitee on Family disclosure. (1998). Statement: Professional disclosure of familial genetic information. *American Journal of Human Genetics, 62*(2), 474-483.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders [DSM-IV]*. Washington, D.C: American Psychiatric Press.

Anderson, D. W., Goldberg, P. A., Algar, U., Felix, R., & Ramesar, R. S. (2007). Mobile colonoscopic surveillance provides quality care for hereditary nonpolyposis colorectal carcinoma families in south africa. *Colorectal Disease, 9*(6), 509-514.

Annie Yu, H. J., Lin, K. M., Ota, D. M., & Lynch, H. T. (2003). Hereditary nonpolyposis colorectal cancer: Preventive management. *Cancer Treatment Reviews, 29*(6), 461-470.

Anwar, S., Hall, C., White, J., Deakin, M., Farrell, W., & Elder, J. B. (2000). Hereditary non-polyposis colorectal cancer: An updated review. *European Journal of Surgical Oncology, 26*(7), 635-645.

Appelbaum, P.S., Ludz, C.W., & Meisel, A. (1987). *Informed consent: Legal theory and Clincal Practice*. New York: Oxford University Press.

Aronson, M. (2009). Genetic counseling for hereditary colorectal cancer: Ethical, legal, and psychosocial issues. *Surgical Oncology Clinics of North America, 18*(4), 669-685.

Arver, B., Haegermark, A., Platten, U., Lindblom, A., & Brandberg, Y. (2004). Evaluation of psychosocial effects of pre-symptomatic testing for breast/ovarian and colon cancer pre-disposing genes: A 12-month follow-up. *Familial Cancer, 3*(2), 109-116.

Ashida, S., Hadley, D. W., Vaughn, B. K., Kuhn, N. R., Jenkins, J. F., & Koehly, L. M. (2009). The impact of familial environment on depression scores after genetic testing for cancer susceptibility. *Clinical Genetics, 75*(1), 43-49.

Baglietto, L., Lindor, N. M., Dowty, J. G., White, D. M., Wagner, A., Gomez Garcia, E. B., et al. (2010). Risks of Lynch syndrome cancers for MSH6 mutation carriers. *Journal of the National Cancer Institute, 102*(3), 193-201.

Baker, D.L., Schutte, J.L., Uhlmann, W.R. (1998). *A guide to genetic counselling*. New York: Wiley-Liss.

Balmana, J., Stoffel, E., Emmons, K., Garber, J., & Syngal, S. (2004). Comparison of motivations and concerns for genetic testing in hereditary colorectal and breast cancer syndromes [Electronic version]. *British Medical Journal, 41*(4), e44. [Retrieved July 2010 from PubMed Online database].

Bank A., Malherbe, C., & van der Spuy, P. (2003). *People of the Western Cape: A history for schools*. Cape Town: Juta Gariep.

Barbour, R. (2008). *Introducing qualitative research: A student guide to the craft of doing qualitative research*. London: SAGE.

Barnetson, R. A., Tenesa, A., Farrington, S. M., Nicholl, I. D., Cetnarskyj, R., Porteous, M. E., et al. (2006). Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *The New England Journal of Medicine, 354*(26), 2751-2763.

Barrow, E., Alduaij, W., Robinson, L., Shenton, A., Clancy, T., Lalloo, F., et al. (2008). Colorectal cancer in HNPCC: Cumulative lifetime incidence, survival and tumour distribution. A report of 121 families with proven mutations. *Clinical Genetics, 74*(3), 233-242.

Barrow, E., Robinson, L., Alduaij, W., Shenton, A., Clancy, T., Lalloo, F., et al. (2009). Cumulative lifetime incidence of extracolonic cancers in lynch

syndrome: A report of 121 families with proven mutations. *Clinical Genetics, 75*(2), 141-149.

Beck, R. B. (2000). *The history of South Africa. Cape Town:* Greenwood Publishing Group.

Beeker, C., Kraft, J. M., Southwell, B. G., & Jorgensen, C. M. (2000). Colorectal cancer screening in older men and women: Qualitative research findings and implications for intervention. *Journal of Community Health, 25*(3), 263-278.

Bellacosa, A., Genuardi, M., Anti, M., Viel, A., & Ponz de Leon, M. (1996). Hereditary nonpolyposis colorectal cancer: Review of clinical, molecular genetics, and counseling aspects. *American Journal of Medical Genetics, 62*(4), 353-364.

Benatar, S. R., & van Rensburg, H. C. (1995). Health care services in a new south africa. *The Hastings Center Report, 25*(4), 16-21.

Bennett, R. L., Hampel, H. L., Mandell, J. B., & Marks, J. H. (2003). Genetic counselors: Translating genomic science into clinical practice. *The Journal of Clinical Investigation, 112*(9), 1274-1279.

Berends, M. J., Wu, Y., Sijmons, R. H., Mensink, R. G., van der Sluis, T., Hordijk-Hos, J. M., et al. (2002). Molecular and clinical characteristics of MSH6 variants: An analysis of 25 index carriers of a germline variant. *American Journal of Human Genetics, 70*(1), 26-37.

Bermejo, J. L., Eng, C., & Hemminki, K. (2005). Cancer characteristics in swedish families fulfilling criteria for hereditary nonpolyposis colorectal cancer. *Gastroenterology, 129*(6), 1889-1899.

Bernhardt, B. A., Biesecker, B. B., & Mastromarino, C. L. (2000). Goals, benefits, and outcomes of genetic counseling: Client and genetic counselor assessment. *Medical Genetics,* 94(3), 189-197.

Biesecker, B. B., & Marteau, T. M. (1999). The future of genetic counselling: An international perspective. *Nature Genetics, 22*(2), 133-137.

Biesecker, B. B., & Peters, K. F. (2001). Process studies in genetic counseling: Peering into the black box. *American Journal of Medical Genetics, 106*(3), 191-198.

Bjorvatn, C., Eide, G. E., Hanestad, B. R., Oyen, N., Havik, O. E., Carlsson, A., et al. (2007). Risk perception, worry and satisfaction related to genetic counseling for hereditary cancer. *Journal of Genetic Counseling, 16*(2), 211-222.

Blandy, C., Chabal, F., Stoppa-Lyonnet, D., & Julian-Reynier, C. (2003). Testing participation in BRCA1/2-positive families: Initiator role of index cases. *Genetic Testing, 7*(3), 225-233.

Bleiker, E. M., Aaronson, N. K., Menko, F. H., Hahn, D. E., van Asperen, C. J., Rutgers, E. J., et al. (1997). Genetic counseling for hereditary cancer: A pilot study on experiences of patients and family members. *Patient Education and Counseling, 32*(1-2), 107-116.

Bleiker, E. M., Hahn, D. E., & Aaronson, N. K. (2003). Psychosocial issues in cancer genetics-current status and future directions. *Acta Oncologica, 42*(4), 276-286.

Bleiker, E. M., Menko, F. H., Taal, B. G., Kluijt, I., Wever, L. D., Gerritsma, M. A., et al. (2005). Screening behavior of individuals at high risk for colorectal cancer. *Gastroenterology, 128*(2), 280-287.

Blokhuis, M. M., Goldberg, P. A., Pietersen, G. E., Algar, U., Vorster, A. A., Govender, D., et al. (2008). The extracolonic cancer spectrum in females with the common 'south african' hMLH1 c.C1528T mutation. *Familial Cancer, 7(3), 191-198.*

Bober, S. L., Hoke, L. A., Duda, R. B., & Tung, N. M. (2007). Recommendation recall and satisfaction after attending breast/ovarian cancer risk counseling. *Journal of Genetic Counseling, 16*(6), 755-762.

Boland, C. R. (2005). Evolution of the nomenclature for the hereditary colorectal cancer syndromes. *Familial Cancer, 4*(3), 211-218.

Boland, C. R., Thibodeau, S. N., Hamilton, S. R., Sidransky, D., Eshleman, J. R., Burt, R. W., et al. (1998). A national cancer institute workshop on microsatellite instability for cancer detection and familial predisposition: Development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Research, 58*(22), 5248-5257.

Bonadona, V., Bonaiti, B., Olschwang, S., Grandjouan, S., Huiart, L., Longy, M., et al. (2011). Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in lynch syndrome. *The Journal of the American Medical Association, 305*(22), 2304-2310.

Bonadona, V., Saltel, P., Desseigne, F., Mignotte, H., Saurin, J. C., Wang, Q., et al. (2002). Cancer patients who experienced diagnostic genetic testing for cancer susceptibility: Reactions and behavior after the disclosure of a positive test result. *Cancer Epidemiology, Biomarkers & Prevention, 11*(1), 97-104.

Borry, P., Stultiens, L., Nys, H., Cassiman, J. J., & Dierickx, K. (2006). Presymptomatic and predictive genetic testing in minors: A systematic review of guidelines and position papers. *Clinical Genetics, 70*(5), 374-381.

Bottorff, J. L., Ratner, P. A., Johnson, J. L., Lovato, C. Y., & Joab, S. A. (1998). Communicating cancer risk information: The challenges of uncertainty. *Patient Education and Counseling, 33*(1), 67-81.

Bradshaw, D., Nannan, N., Groenewald, P., Joubert, J., Laubscher, R., Nojilana, B., et al. (2005). Provincial mortality in south africa, 2000–priority-setting for now and a benchmark for the future. *South African Medical Journal, 95*(7), 496-503.

Bradshaw, D., Nannan, N., Laubscher, R., Groenewald, P., Joubert, J., Nojilana, B., et al. (2004) *South African national burden of disease study 2000: Estimates of provincial mortality*. Cape Town: South African Medical Research Council.

Bradstock, A. (2005). Changing livelihoods and land reform: Evidence from the northern cape province of south africa. *World Development, 33*(11), 1979-1992.

Brain, K., Sivell, S., Bennert, K., Howell, L., France, L., Jordan, S., et al. (2005). An exploratory comparison of genetic counselling protocols for HNPCC predictive testing. *Clinical Genetics, 68*(3), 255-261.

Brink, H. (1996). *Fundamentals of research methodology for health care professionals*. Cape Town: Juta and Company Ltd.

Broadhead, R. S. (1980). Qualitative analysis in evaluation research: Problems and promises of an interactionist approach. *Symbolic Interaction, 3*(1), 23-40.

Broadstock, M., Michie, S., & Marteau, T. (2000). Psychological consequences of predictive genetic testing: A systematic review. *European Journal of Human Genetics, 8*(10), 731-738.

Burgard, S. A., & Treiman, D. J. (2006). Trends and racial differences in infant mortality in south africa. *Social Science & Medicine (1982), 62*(5), 1126-1137.

Burger, D. (2009). *The land and its people: South African yearbook 2008/09*. Pretoria: Government Communication and information system.

Burn, J., Bishop, D. T., Mecklin, J. P., Macrae, F., Moslein, G., Olschwang, S., et al. (2008). Effect of aspirin or resistant starch on colorectal neoplasia in the lynch syndrome. *The New England Journal of Medicine, 359*(24), 2567-2578.

Burton, A. M., Peterson, S. K., Marani, S. K., Vernon, S. W., Amos, C. I., Frazier, M. L., et al. (2010). Health and lifestyle behaviors among persons at risk of lynch syndrome. *Cancer Causes & Control, 21*(4), 513-521.

Cai, S. J., Xu, Y., Cai, G. X., Lian, P., Guan, Z. Q., Mo, S. J., et al. (2003). Clinical characteristics and diagnosis of patients with hereditary nonpolyposis colorectal cancer. *World Journal of Gastroenterology, 9*(2), 284-287.

Caluseriu, O., Di Gregorio, C., Lucci-Cordisco, E., Santarosa, M., Trojan, J., Brieger, A., et al. (2004). A founder MLH1 mutation in families from the districts of modena and reggio-emilia in northern italy with hereditary non-polyposis colorectal cancer associated with protein elongation and instability [Electronic version]. *Journal of Medical Genetics, 41*(3), e34. [Retrieved May 2010 from PubMed Online database].

Campos, F.G., Logullo Waitzberg, A.G., Kiss, D.R., Waitzberg, D.L., Habr-Gama, A., Gama-Rodrigues, J. (2005). Diet and colorectal cancer: current evidence for etiology and prevention. *Nutricion Hospitalaria,* 20(1), 18-25.

CANSA Registry. (1997). *Colorectal cancer: numbers and incidence.* Retrieved February 2009 from http://www.cansa.org.za/Research/registry1997_colorectal.asp.

Carpenter, C., & Suto, M. (2008). *Qualitative research for occupational and physical therapists: A practical guide.* Blackwell Publishing: Oxford.

Cederquist, K., Emanuelsson, M., Wiklund, F., Golovleva, I., Palmqvist, R., & Gronberg, H. (2005). Two swedish founder MSH6 mutations, one nonsense and one missense, conferring high cumulative risk of lynch syndrome. *Clinical Genetics, 68*(6), 533-541.

Chan, T. L., Chan, Y. W., Ho, J. W., Chan, C., Chan, A. S., Chan, E., et al. (2004). MSH2 c.1452-1455delAATG is a founder mutation and an important cause of hereditary nonpolyposis colorectal cancer in the southern chinese population. *American Journal of Human Genetics, 74*(5), 1035-1042.

Chapman, P. D., & Burn, J. (1999). Genetic predictive testing for bowel cancer predisposition: The impact on the individual. *Cytogenetics and Cell Genetics, 86*(2), 118-124.

Charles, S., Kessler, L., Stopfer, J. E., Domchek, S., & Halbert, C. H. (2006). Satisfaction with genetic counseling for BRCA1 and BRCA2 mutations among african american women. *Patient Education and Counseling, 63*(1-2), 196-204.

Chen, H. T., & Rossi, P. H. (1983). Evaluating with sense: The theory-driven approach. *Evaluation Review, 7*(3), 283-302.

Chen, L. M., Yang, K. Y., Little, S. E., Cheung, M. K., & Caughey, A. B. (2007). Gynecologic cancer prevention in lynch syndrome/hereditary nonpolyposis colorectal cancer families. *Obstetrics and Gynecology, 110*(1), 18-25.

Claes, E., Evers-Kiebooms, G., Boogaerts, A., Decruyenaere, M., Denayer, L., & Legius, E. (2003). Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. *American Journal of Medical Genetics, 116*(1), 11-19.

Claes, E., Denayer, L., Evers-Kiebooms, G., Boogaerts, A., & Legius, E. (2004). Predictive testing for hereditary non-polyposis colorectal cancer: Motivation, illness representations and short-term psychological impact. *Patient Education and Counseling, 55*(2), 265-274.

Codori, A. M., Petersen, G. M., Miglioretti, D. L., & Boyd, P. (2001). Health beliefs and endoscopic screening for colorectal cancer: Potential for cancer prevention. *Preventive Medicine, 33*(2 Pt 1), 128-136.

Codori, A. M., Petersen, G. M., Miglioretti, D. L., Larkin, E. K., Bushey, M. T., Young, C., et al. (1999). Attitudes toward colon cancer gene testing: Factors predicting test uptake. *Cancer Epidemiology, Biomarkers & Prevention, 8*(4 Pt 2), 345-351.

Cohen, M. Z., & Omery, A. (1994). Schools of phenomenology: Implications for research. In J.M. Morse (Ed.). *Critical Issues in Qualitative Research Methods*, 136-156. Thousand Oaks, California: Sage.

Colaizzi, P. (1978). Psychological research as the phenomenologist views it. In R. Valle & M. King (Ed). *Existential-phenomenological alternatives for psychology*. New York: Oxford University Press.

Collins, V., Halliday, J., Warren, R., & Williamson, R. (2000). Cancer worries, risk perceptions and associations with interest in DNA testing and clinic satisfaction in a familial colorectal cancer clinic. *Clinical Genetics, 58*(6), 460-468.

Collins, V., Meiser, B., Gaff, C., St John, D., & Halliday, J. (2005). Screening and preventive behaviors one year after predictive genetic testing for hereditary nonpolyposis colorectal carcinoma. *Cancer, 104*(2), 273–281.

Collins, V., Meiser, B., Ukoumunne, O. C., Gaff, C., St John, D. J., & Halliday, J. L. (2007). The impact of predictive genetic testing for hereditary nonpolyposis colorectal cancer: Three years after testing. *Genetics in Medicine, 9*(5), 290-297.

Committee for public relations and ethical issues of the German Society of Human Genetics. (2000). *Positional paper of the German Society of Human Genetics*, 1–13.

Coovadia, H., Jewkes, R., Barron, P., Sanders, D., & McIntyre, D. (2009). The health and health system of south africa: Historical roots of current public health challenges. *Lancet, 374*(9692), 817-834.

Cornaggia, M., Tibiletti, M. G., Albarello, L., Taborelli, M., Dalla Longa, E., & Capella, C. (2000). Low incidence of hereditary nonpolyposis colorectal cancer syndrome in a selected area of the lombardy cancer registry. *Tumori, 86*(6), 439-444.

Crockett, D. G., Wagner, D. G., Holmang, S., Johansson, S. L., & Lynch, H. T. (2011). Upper urinary tract carcinoma in lynch syndrome cases. *The Journal of Urology, 185*(5), 1627-1630.

Cronin ,P., Ryan, F., Coughlan, M. (2010). Concept analysis in healthcare research. *International journal of therapy and rehabilitation*, 17(2), 62-68.

Cronjé, L., Paterson, A., & Becker, P. (2009). Colorectal cancer in south africa: A heritable cause suspected in many young black patients. *South African Medical Journal,* 99(2), 103-106.

Croyle, R. T., & Lerman, C. (1993). Interest in genetic testing for colon cancer susceptibility: Cognitive and emotional correlates. *Preventive Medicine, 22*(2), 284-292.

Cunningham, J. M., Kim, C. Y., Christensen, E. R., Tester, D. J., Parc, Y., Burgart, L. J., et al. (2001). The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. *American Journal of Human Genetics, 69*(4), 780-790.

d'Agincourt-Canning, L. (2001). Experiences of genetic risk: Disclosure and the gendering of responsibility. *Bioethics, 15*(3), 231-247.

Daly J., Kellehear, .A, Gliksman, M. (1997). *The public health researcher: A methodological guide*. New York: Oxford University Press.

Davey, A., Rostant, K., Harrop, K., Goldblatt, J., & O'Leary, P. (2005). Evaluating genetic counseling: Client expectations, psychological adjustment and satisfaction with service. *Journal of Genetic Counseling, 14*(3), 197-206.

de Jong, A. E., Morreau, H., Van Puijenbroek, M., Eilers, P. H., Wijnen, J., Nagengast, F. M., et al. (2004). The role of mismatch repair gene defects in the development of adenomas in patients with HNPCC. *Gastroenterology, 126*(1), 42-48.

de Jong, A. E., Nagengast, F. M., Kleibeuker, J. H., van de Meeberg, P. C., van Wijk, H. J., Cats, A., et al. (2006). What is the appropriate screening protocol in lynch syndrome? *Familial Cancer, 5*(4), 373-378.

de Leeuw, W. J., Dierssen, J., Vasen, H. F., Wijnen, J. T., Kenter, G. G., Meijers-Heijboer, H., et al. (2000). Prediction of a mismatch repair gene defect by microsatellite instability and immunohistochemical analysis in endometrial tumours from HNPCC patients. *The Journal of Pathology, 192*(3), 328-335.

Denscombe, M. (2008). *The good research guide for small-scale research projects* (3rd Edn). Berkshire: Open University Press.

Department of Health. (NO DATE). *Mission and Vision*. Retrieved April 2010 from http://www.doh.gov.za/.

Department of Trade and Industry RSA. (2006). *South Africa's economic transformation*. Retrieved March 2010 from http://www.dti.gov.za/bee/bee.htm.

de Vos tot Nederveen Cappel,W.H., Nagengast, F. M., Griffioen, G., Menko, F. H., Taal, B. G., Kleibeuker, J. H., et al. (2002). Surveillance for hereditary nonpolyposis colorectal cancer: A long-term study on 114 families. *Diseases of the Colon and Rectum, 45*(12), 1588-1594.

de Wert, G. (1998). Ethics of predictive DNA-testing for hereditary breast and ovarian cancer. *Patient Education and Counseling, 35*(1), 43-52.

de Wert, G. (1998). Ethics of predictive DNA-testing for hereditary breast and ovarian cancer. *Patient Education and Counseling, 35*(1), 43-52.

DeMarco, T. A., Peshkin, B. N., Mars, B. D., & Tercyak, K. P. (2004). Patient satisfaction with cancer genetic counseling: A psychometric analysis of the genetic counseling satisfaction scale. *Journal of Genetic Counseling, 13*(4), 293-304.

Denberg, T. D., Melhado, T. V., Coombes, J. M., Beaty, B. L., Berman, K., Byers, T. E., et al. (2005). Predictors of nonadherence to screening colonoscopy. *Journal of General Internal Medicine,* 20(11), 989-995.

Desai, D. C., Lockman, J. C., Chadwick, R. B., Gao, X., Percesepe, A., Evans, D. G. R., et al. (2000). Recurrent germline mutation in MSH2 arises frequently de novo. *British Medical Journal, 37*(9), 646.

Dewanwala, A., Chittenden, A., Rosenblatt, M., Mercado, R., Garber, J. E., Syngal, S., et al. (2011). Attitudes toward childbearing and prenatal testing in individuals undergoing genetic testing for lynch syndrome [Electronic version]. *Familial Cancer. [Retrieved July 2011 from PubMed Online database].*

Diergaarde, B., Braam, H., Vasen, H. F., Nagengast, F. M., van Muijen, G. N., Kok, F. J., et al. (2007). Environmental factors and colorectal tumor risk in individuals with hereditary nonpolyposis colorectal cancer. *Clinical Gastroenterology and Hepatology, 5*(6), 736-742.

Doak, C. C., Doak, L. G., Friedell, G. H., & Meade, C. D. (1998). Improving comprehension for cancer patients with low literacy skills: Strategies for clinicians. *A Cancer Journal for Clinicians, 48*(3), 151-162.

Domanska, K., Carlsson, C., Bendahl, P. O., & Nilbert, M. (2009). Knowledge about hereditary nonpolyposis colorectal cancer; mutation carriers and physicians at equal levels. [Electronic version]. *BMC Medical Genetics, 10*(30). [*Retrieved March 2009 from BioMed Central Online databse].*

Domingo, E., Laiho, P., Ollikainen, M., Pinto, M., Wang, L., French, A. J., et al. (2004). BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. *Journal of Medical Genetics, 41*(9), 664-668.

Dores, G. M., Curtis, R. E., Toro, J. R., Devesa, S. S., & Fraumeni, J. F.,Jr. (2008). Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: Insight into muir-torre syndrome. *Cancer, 113*(12), 3372-3381.

Dorval, M., Patenaude, A. F., Schneider, K. A., Kieffer, S. A., DiGianni, L., Kalkbrenner, K. J., et al. (2000). Anticipated versus actual emotional reactions to disclosure of results of genetic tests for cancer susceptibility: Findings from p53 and BRCA1 testing programs. *Journal of Clinical Oncology, 18*(10), 2135-2142.

Douglas, J. A., Gruber, S. B., Meister, K. A., Bonner, J., Watson, P., Krush, A. J., et al. (2005). History and molecular genetics of lynch syndrome in family G: A century later. *The Journal of the American Medical Association, 294*(17), 2195-2202.

Dove-Edwin, I., Boks, D., Goff, S., Kenter, G. G., Carpenter, R., Vasen, H. F., et al. (2002). The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer, 94*(6), 1708-1712.

Dugan, R. B., Wiesner, G. L., Juengst, E. T., O'Riordan, M., Matthews, A. L., & Robin, N. H. (2003). Duty to warn at-risk relatives for genetic disease: Genetic counselors' clinical experience. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 119C*(1), 27-34.

Dunlop, M. G., Farrington, S. M., Carothers, A. D., Wyllie, A. H., Sharp, L., Burn, J., et al. (1997). Cancer risk associated with germline DNA mismatch repair gene mutations. *Human Molecular Genetics, 6*(1), 105-110.

Elwyn, G., Gray, J., & Clarke, A. (2000). Shared decision making and non-directiveness in genetic counselling. *Journal of Medical Genetics, 37*(2), 135-138.

Engel, C., Rahner, N., Schulmann, K., Holinski-Feder, E., Goecke, T. O., Schackert, H. K., et al. (2010). Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clinical Gastroenterology and Hepatology, 8*(2), 174-182.

Ensenauer, R. E., Michels, V. V., & Reinke, S. S. (2005). Genetic testing: Practical, ethical, and counseling considerations. *Mayo Clinic Proceedings. Mayo Clinic, 80*(1), 63-73.

Equal Employment Opportunity Commission. (1995). *Compliance Manual*. Volume 2, Section 902 Order 915.002.

Erasmus, Z. (2001). *Coloured by history shaped by place: New perspectives on Coloured identities in Cape Town*. Cape Town: Kwela Books.

Erblich, J., Brown, K., Kim, Y., Valdimarsdottir, H. B., Livingston, B. E., & Bovbjerg, D. H. (2005). Development and validation of a breast cancer genetic counseling knowledge questionnaire. *Patient Education and Counseling, 56*(2), 182-191.

Ersig, A. L., Hadley, D. W., & Koehly, L. M. (2009). Colon cancer screening practices and disclosure after receipt of positive or inconclusive genetic test results for hereditary nonpolyposis colorectal cancer. *Cancer, 115*(18), 4071-4079.

Esplen, M. J., Madlensky, L., Butler, K., McKinnon, W., Bapat, B., Wong, J., et al. (2001). Motivations and psychosocial impact of genetic testing for HNPCC. *American Journal of Medical Genetics, 103*(1), 9-15.

Esplen, M. J., Madlensky, L., Aronson, M., Rothenmund, H., Gallinger, S., Butler, K., et al. (2007). Colorectal cancer survivors undergoing genetic testing for hereditary non-polyposis colorectal cancer: Motivational factors and psychosocial functioning. *Clinical Genetics, 72*(5), 394-401.

Esplen, M. J., Urquhart, C., Butler, K., Gallinger, S., Aronson, M., & Wong, J. (2003). The experience of loss and anticipation of distress in colorectal cancer patients undergoing genetic testing. *Journal of Psychosomatic Research, 55*(5), 427-435.

European commission. (2004). *Ethical, legal and social aspects of genetic testing: Research, development and clinical applications*. Luxemburg: European Commission.

Evans, C. (2006). *Genetic counseling. A psychological approach*. New York: Cambridge University Press.

Evans, D.G., Binchy, .A, Shenton, A., Hopwood, P. Craufurd, D. (2009). Coparison of proactive and usual approaches to offering predictive testing for BRCA1/2 mutations in unaffected relatives. *Clinical Genetics*, 75(2), 124-132.

Evans, D. G., Walsh, S., Jeacock, J., Robinson, C., Hadfield, L., Davies, D. R., et al. (1997). Incidence of hereditary non-polyposis colorectal cancer in a population-based study of 1137 consecutive cases of colorectal cancer. *The British Journal of Surgery, 84*(9), 1281-1285.

Evans, J. P., Skrzynia, C., & Burke, W. (2001). The complexities of predictive genetic testing. *British Medical Journal, 322*(7293), 1052-1056.

Evers-Kiebooms, G., Welkenhuysen, M., Claes, E., Decruyenaere, M., & Denayer, L. (2000). The psychological complexity of predictive testing for late onset neurogenetic diseases and hereditary cancers: Implications for multidisciplinary counselling and for genetic education. *Social Science & Medicine, 51*(6), 831-841.

Falk, M. J., Dugan, R. B., O'Riordan, M. A., Matthews, A. L., & Robin, N. H. (2003). Medical geneticists' duty to warn at-risk relatives for genetic disease. *American Journal of Medical Genetics. Part A, 120A*(3), 374-380.

Felix, R., Bodmer, W., Fearnhead, N. S., van der Merwe, L., Goldberg, P., & Ramesar, R. S. (2006). GSTM1 and GSTT1 polymorphisms as modifiers of age at diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC) in a homogeneous cohort of individuals carrying a single predisposing mutation. *Mutation Research, 602*(1-2), 175-181.

Ferreira, A. (2010). Diamond in the dust for local art. *Sunday Times Newspaper*, 25 April. Retrieved May 2010 from http://www.timeslive.co.za/sundaytimes/article418944.ece/Diamond-in-the-dust-for-local-art.

Forrest, K., Simpson, S., Wilson, B., van Teijlingen, E., McKee, L., Haites, N., et al. (2003). To tell or not to tell: Barriers and facilitators in family communication about genetic risk. *Clinical Genetics, 64*(4), 317-326.

Forrest, L. E., Delatycki, M. B., Skene, L., & Aitken, M. (2007). Communicating genetic information in families-a review of guidelines and position papers. *European Journal of Human Genetics, 15*(6), 612-618.

Foster, C., Eeles, R., Ardern-Jones, A., Moynihan, C., & Watson, M. (2004). Juggling roles and expectations: Dilemmas faced by women talking to relatives about cancer and genetic testing. *Psychology and Health, 19*(4), 439-455.

Foulkes, W. D., Thiffault, I., Gruber, S. B., Horwitz, M., Hamel, N., Lee, C., et al. (2002). The founder mutation MSH2*1906G-->C is an important cause of

hereditary nonpolyposis colorectal cancer in the ashkenazi jewish population. *American Journal of Human Genetics, 71*(6), 1395-1412.

Fraser, F. C. (1974). Genetic counseling. *American Journal of Human Genetics, 26*(5), 636-659.

Froggatt, N. J., Green, J., Brassett, C., Evans, D. G., Bishop, D. T., Kolodner, R., et al. (1999). A common MSH2 mutation in english and north american HNPCC families: Origin, phenotypic expression, and sex specific differences in colorectal cancer. *Journal of Medical Genetics, 36*(2), 97-102.

Gaff, C. L., Collins, V., Symes, T., & Halliday, J. (2005). Facilitating family communication about predictive genetic testing: Probands' perceptions. *Journal of Genetic Counseling, 14*(2), 133-140.

Geary, J., Sasieni, P., Houlston, R., Izatt, L., Eeles, R., Payne, S. J., et al. (2008). Gene-related cancer spectrum in families with hereditary non-polyposis colorectal cancer (HNPCC). *Familial Cancer, 7*(2), 163-172.

Geller, G., Botkin, J. R., Green, M. J., Press, N., Biesecker, B. B., Wilfond, B., et al. (1997). Genetic testing for susceptibility to adult-onset cancer. the process and content of informed consent. *The Journal of the American Medical Association, 277*(18), 1467-1474.

Genereviews. (2006). *Hereditary-nonpolyposis colorectal cancer*. Retrieved December 2009 from http://www.ncbi.nlm.nih.gov/books/NBK1211/.

Gili, M., Roca, M., Ferrer, V., Obrador, A., & Cabeza, E. (2006). Psychosocial factors associated with the adherence to a colorectal cancer screening program. *Cancer Detection and Prevention, 30*(4), 354-360.

Giovannucci, E., Stampfer, M. J., Colditz, G., Rimm, E. B., & Willett, W. C. (1992). Relationship of diet to risk of colorectal adenoma in men. *Journal of the National Cancer Institute, 84*(2), 91-98.

Glanz, K., Grove, J., Lerman, C., Gotay, C., & Le Marchand, L. (1999). Correlates of intentions to obtain genetic counseling and colorectal cancer gene testing among at-risk relatives from three ethnic groups. *Cancer Epidemiology, Biomarkers & Prevention, 8*(4 Pt 2), 329-336.

Golafshani, N. (2003). Understanding reliability and validity in qualitative research. *Test,* 8(4), 597-606.

Goldberg, P. A., Madden, M. V., Harocopos, C., Felix, R., Westbrook, C., & Ramesar, R. S. (1998). In a resource-poor country, mutation identification has the potential to reduce the cost of family management for hereditary nonpolyposis colorectal cancer. *Diseases of the Colon and Rectum, 41*(10), 1250-1253.

Goldblatt, J., Madden, M. V., Boshoff, P. J., Wallis, C., & Price, S. K. (1990). Hereditary non-polyposis colorectal cancer in a namaqualand kindred. *South African Medical Journal, 77*(1), 42-44.

Goldin, I. (1987). *Making of race: The politics and economics of Coloured identity in South Africa*. Cape Town: Maskew Miller Longman.

Goodfellow, P. J., Buttin, B. M., Herzog, T. J., Rader, J. S., Gibb, R. K., Swisher, E., et al. (2003). Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers. *Proceedings of the National Academy of Sciences of the United States of America, 100*(10), 5908-5913.

Government Gazette of the Republic of South Africa. (1998). *Act No R417 of 1998*. Pretoria: Government Printers.

Government Gazette of the Republic of South Africa (1992). *Act No 52 of 1992*. Pretoria: Government Printers.

Graham, E.E., Barbato, C.A., & Perse, E.M. (1993). The interpersonal communication motives model. *Communication Quarterly, 41*(2), 172-186.

Gramling, R., Anthony, D., Frierson, G., & Bowen, D. (2007). The cancer worry chart: A single-item screening measure of worry about developing breast cancer. *Psycho-Oncology, 16*(6), 593-597.

Green, J., Richards, M., Murton, F., Statham, H., & Hallowell, N. (1997). Family communication and genetic counseling: The case of hereditary breast and ovarian cancer. *Journal of Genetic Counseling, 6*(1), 45-60.

Gritz, E. R., Peterson, S. K., Vernon, S. W., Marani, S. K., Baile, W. F., Watts, B. G., et al. (2005). Psychological impact of genetic testing for hereditary nonpolyposis colorectal cancer. *Journal of Clinical Oncology, 23*(9), 1902-1910.

Groenewegen, P. P., Kerssens, J. J., Sixma, H. J., van der Eijk, I., & Boerma, W. G. (2005). What is important in evaluating health care quality? an international comparison of user views. [Electronic version]. *BMC Health Services*

Research, 5(1). [Retrieved April 2009 from BioMed Central Online database].

Gryfe, R., Kim, H., Hsieh, E. T., Aronson, M. D., Holowaty, E. J., Bull, S. B., et al. (2000). Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *The New England Journal of Medicine, 342*(2), 69-77.

Guerra, C. E., Dominguez, F., & Shea, J. A. (2005). Literacy and knowledge, attitudes, and behavior about colorectal cancer screening. *Journal of Health Communication, 10*(7), 651-663.

Hadley, D. W., Ashida, S., Jenkins, J. F., Calzone, K. A., Kirsch, I. R., & Koehly, L. M. (2011). Colonoscopy use following mutation detection in lynch syndrome: Exploring a role for cancer screening in adaptation. *Clinical Genetics, 79*(4), 321-328.

Hadley, D. W., Jenkins, J., Dimond, E., Nakahara, K., Grogan, L., Liewehr, D. J., et al. (2003). Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. *Archives of Internal Medicine, 163*(5), 573-582.

Hadley, D. W., Jenkins, J. F., Dimond, E., de Carvalho, M., Kirsch, I., & Palmer, C. G. S. (2004). Colon cancer screening practices after genetic counseling and testing for hereditary nonpolyposis colorectal cancer. *Journal of Clinical Oncology, 22*(1), 39.

Halbert, C. H., Lynch, H., Lynch, J., Main, D., Kucharski, S., Rustgi, A. K., et al. (2004). Colon cancer screening practices following genetic testing for hereditary nonpolyposis colon cancer (HNPCC) mutations. *Archives of Internal Medicine, 164*(17), 1881-1887.

Hallowell, N., Murton, F., Statham, H., Green, J., & Richards, M. (1997). Women's need for information before attending genetic counselling for familial breast or ovarian cancer: A questionnaire, interview, and observational study. *British Medical Journal, 314*(7076), 281-283.

Hampel, H., Frankel, W. L., Martin, E., Arnold, M., Khanduja, K., Kuebler, P., et al. (2008). Feasibility of screening for lynch syndrome among patients with colorectal cancer. *Journal of Clinical Oncology, 26*(35), 5783-5788.

Hampel, H., Frankel, W. L., Martin, E., Arnold, M., Khanduja, K., Kuebler, P., et al. (2005a). Screening for the lynch syndrome (hereditary nonpolyposis

colorectal cancer). *The New England Journal of Medicine, 352*(18), 1851-1860.

Hampel, H., Stephens, J. A., Pukkala, E., Sankila, R., Aaltonen, L. A., Mecklin, J. P., et al. (2005b). Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: Later age of onset. *Gastroenterology, 129*(2), 415-421.

Harper, P.S. (1998). *Practical genetic counselling*. Oxford: ButterworthHeinemann.

Harris, M. A., & Byles, J. E. (1997). A survey of screening compliance among first degree relatives of people with colon cancer in new south wales. *Journal of Medical Screening, 4*(1), 29-34.

Hendriks, Y. M., Wagner, A., Morreau, H., Menko, F., Stormorken, A., Quehenberger, F., et al. (2004). Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: Impact on counseling and surveillance. *Gastroenterology, 127*(1), 17-25.

Holloway, I. (1997). *Basic concepts for qualitative research*. Oxford: Blackwell Science.

Holloway, I. (2005). *Qualitative research in health care.* New York: University Press McGraw Hill.

Holloway, I. & Wheeler, S. (1996). *Qualitative research for nurses*. Oxford: Blackwell Science.

Hopwood, P. (1997). Psychological issues in cancer genetics: Current research and future priorities. *Patient Education and Counseling, 32*(1-2), 19-31.

Houlston, R. S., Murday, V., Harocopos, C., Williams, C. B., & Slack, J. (1990). Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. *British Medical Journal, 301*(6748), 366-368.

Hughes, C., Lerman, C., Schwartz, M., Peshkin, B. N., Wenzel, L., Narod, S., et al. (2002). All in the family: Evaluation of the process and content of sisters' communication about BRCA1 and BRCA2 genetic test results. *American Journal of Medical Genetics, 107*(2), 143-150.

Hughes, C., Lynch, H., Durham, C., Snyder, C., Lemon, S., Narod, S., et al. (1999). Communication of BRCA1/2 test results in hereditary breast cancer families. *Cancer Research, Therapy and Control, 8*(1-2), 51-59.

INSIGHT. (2008): International society for gastroenterological tumours. Retrieved April 2010 from http://www.insight-group.org/mutations/.

Irmejs, A., Borosenko, V., Melbarde-Gorkusa, I., Gardovskis, A., Bitina, M., Kurzawski, G., et al. (2007). Nationwide study of clinical and molecular features of hereditary non-polyposis colorectal cancer (HNPCC) in latvia. *Anticancer Research, 27*(1B), 653-658.

Itoh, H., Houlston, R. S., Harocopos, C., & Slack, J. (1990). Risk of cancer death in first-degree relatives of patients with hereditary non-polyposis cancer syndrome (lynch type II): A study of 130 kindreds in the united kingdom. *The British Journal of Surgery, 77*(12), 1367-1370.

Järvinen, H. J., Aarnio, M., Mustonen, H., Aktan-Collan, K., Aaltonen, L. A., Peltomaki, P., et al. (2000). Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology, 118*(5), 829-834.

Järvinen, H. J., Mecklin, J. P., & Sistonen, P. (1995). Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology, 108*(5), 1405-1411.

Järvinen, H. J., Renkonen-Sinisalo, L., Aktan-Collan, K., Peltomaki, P., Aaltonen, L. A., & Mecklin, J. P. (2009). Ten years after mutation testing for lynch syndrome: Cancer incidence and outcome in mutation-positive and mutation-negative family members. *Journal of Clinical Oncology, 27*(28), 4793-4797.

Jass, J., Stewart, S., Schroeder, D., & Lane, M. (1992). Screening for hereditary non-polyposis colorectal cancer in new zealand. *European Journal of Gastroenterology & Hepatology, 4*(7), 523-527.

Jass, J. R. (2007). Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology, 50*(1), 113-130.

Jass, J. R., & Stewart, S. M. (1992). Evolution of hereditary non-polyposis colorectal cancer. *Gut, 33*(6), 783-786.

Jawień, A., Banaszkiewicz, Z., & Carcinoma, C. (1998). Incidence of hereditary non-polyposis colorectal cancer (HNPCC)—personal experience. *Medical Science Monitor, 4*(6), 1009-1011.

Jenkins, M. A., Baglietto, L., Dowty, J. G., Van Vliet, C. M., Smith, L., Mead, L. J., et al. (2006). Cancer risks for mismatch repair gene mutation carriers: A

population-based early onset case-family study. *Clinical Gastroenterology and Hepatology, 4*(4), 489-498.

Johnstone F.A. (1976). *Class, race and gold: A study of class relations and racial discrimination in South Africa*. New York: University Press of America.

Jones, L. S., Nicholson, R. W., & Evans, D. A. (2001). Experience with a one-stop colorectal clinic. *Journal of the Royal College of Surgeons of Edinburgh, 46*(2), 96-97.

Jorde, L. B. (2001). Consanguinity and prereproductive mortality in the utah mormon population. *Human Heredity, 52*(2), 61-65.

Jorde, L.B., Carey, J.C., Bamshad, M.J., White, R.L. (2006). Medical genetics (3rd Edn). Philadelphia: Mosby.

Julian-Reynier, C., Eisinger, F., Chabal, F., Lasset, C., Nogues, C., Stoppa-Lyonnet, D., et al. (2000). Disclosure to the family of breast/ovarian cancer genetic test results: Patient's willingness and associated factors. *American Journal of Medical Genetics, 94*(1), 13-18.

Julian-Reynier, C., Eisinger, F., Vennin, P., Chabal, F., Aurran, Y., Nogues, C., et al. (1996). Attitudes towards cancer predictive testing and transmission of information to the family. *Journal of Medical Genetics, 33*(9), 731-736.

Kasparian, N. A., Wakefield, C. E., & Meiser, B. (2007). Assessment of psychosocial outcomes in genetic counseling research: An overview of available measurement scales. *Journal of Genetic Counseling, 16*(6), 693-712.

Kastrinos, F., Stoffel, E. M., Balmana, J., Steyerberg, E. W., Mercado, R., & Syngal, S. (2008). Phenotype comparison of MLH1 and MSH2 mutation carriers in a cohort of 1,914 individuals undergoing clinical genetic testing in the united states. *Cancer Epidemiology, Biomarkers & Prevention, 17*(8), 2044-2051.

Katballe, N., Christensen, M., Wikman, F. P., Orntoft, T. F., & Laurberg, S. (2002). Frequency of hereditary non-polyposis colorectal cancer in danish colorectal cancer patients. *Gut, 50*(1), 43-51.

Katballe, N., Juul, S., Christensen, M., Orntoft, T. F., Wikman, F. P., & Laurberg, S. (2001). Patient accuracy of reporting on hereditary non-polyposis colorectal cancer-related malignancy in family members. *The British Journal of Surgery, 88*(9), 1228-1233.

Kausmeyer, D. T., Lengerich, E. J., Kluhsman, B. C., Morrone, D., Harper, G. R., & Baker, M. J. (2006). A survey of patients‘ experiences with the cancer genetic counseling process: Recommendations for cancer genetics programs. *Journal of Genetic Counseling, 15*(6), 409-431.

Kee, F., & Collins, B. J. (1991). How prevalent is cancer family syndrome? *Gut, 32*(5), 509-512.

Keenan, K., Simpson, S., Wilson, B., Van Teijlingen, E., Mckee, L., Haites, N., et al. (2005). It's their blood not mine': Who's responsible for (not) telling relatives about genetic risk? *Health, Risk & Society, 7*(3), 209-226.

Keller, M., Jost, R., Kadmon, M., Wullenweber, H. P., Haunstetter, C. M., Willeke, F., et al. (2004). Acceptance of and attitude toward genetic testing for hereditary nonpolyposis colorectal cancer: A comparison of participants and nonparticipants in genetic counseling. *Diseases of the Colon and Rectum, 47*(2), 153-162.

Kelly, T.E. (1986). *Clinical genetics and genetic counselling*, 343-364. Chicago: Year book medical publishers.

Kessler, S. (1979). Introduction. In: S. Kessler (Ed). *Genetic counseling: psychological dimensions*, 1-15. New York: Academic press.

Kessler, S. (1989). Psychological aspects of genetic counseling: VI. A critical review of the literature dealing with education and reproduction. *American Journal of Medical Genetics, 34*(3), 340-353.

Kessler, S. (1997). Psychological aspects of genetic counseling. XI. Nondirectiveness revisited. *American Journal of Medical Genetics, 72*(2), 164-171.

Kinney, A. Y., Choi, Y. A., DeVellis, B., Kobetz, E., Millikan, R. C., & Sandler, R. S. (2000). Interest in genetic testing among first-degree relatives of colorectal cancer patients. *American Journal of Preventive Medicine, 18*(3), 249-252.

Koch, T. (1995). Interpretive approaches in nursing research: The influence of husserl and heidegger. *Journal of Advanced Nursing, 21*(5), 827-836.

Koehly, L. M., Peterson, S. K., Watts, B. G., Kempf, K. K. G., Vernon, S. W., & Gritz, E. R. (2003). A social network analysis of communication about hereditary nonpolyposis colorectal cancer genetic testing and family functioning. *Cancer Epidemiology Biomarkers & Prevention, 12*(4), 304-313.

Kohut, K., Manno, M., Gallinger, S., & Esplen, M. J. (2007). Should healthcare providers have a duty to warn family members of individuals with an HNPCC-causing mutation? A survey of patients from the ontario familial colon cancer registry. *British Medical Journal, 44*(6), 404-407.

Kolonel, L., Hinds, M., & Hankin, J. (1980). Cancer patterns among migrant and native-born japanese in hawaii in relation to smoking, drinking, and dietary habits. In: H.V Gelbion, B. MacMohan, T. Matsushima, S. Sugimura, H Takebe (Ed). *Genetic and Environmental Factors in Experimental and Human Cancer,* 327-340. Tokyo: Japan Scientific Societies Press.

Knaack, P. (1984). Phenomenological research. *Western Journal of Nursing Research*, 6(1), 107-123.

Koornstra, J. J., Mourits, M. J., Sijmons, R. H., Leliveld, A. M., Hollema, H., & Kleibeuker, J. H. (2009). Management of extracolonic tumours in patients with lynch syndrome. *The Lancet Oncology, 10*(4), 400-408.

Kruger, B.J. (2005). *Hereditary nonpolyposis colorectal cancer: Factors contributing to adherence and non-adherence to surveillance for mutation carriers in rural areas of the northern and western cape*. Master's thesis. University of Cape Town, South Africa.

Laghi, L., Bianchi, P., Roncalli, M., & Malesci, A. (2004). Re: Revised bethesda guidelines for hereditary nonpolyposis colorectal cancer (lynch syndrome) and microsatellite instability. *Journal of the National Cancer Institute, 96*(18), 1402-1403.

Lalloo, R., Myburgh, N. G., Smith, M. J., & Solanki, G. C. (2004). Access to health care in south africa--the influence of race and class. *South African Medical Journal, 94*(8), 639-642.

Lambert, R. (1983). Principles of screening adapted to precancerous conditions of the gastrointestinal tract. In P. Sherlock, B.C. Morson, L. Barbara, U. Veronesi (Ed). *Precancerous Lesions of the Gastrointestinal Tract,* 292-303. New York: Raven Press.

Lastella, P., Patruno, M., Forte, G., Montanaro, A., Di Gregorio, C., Sabba, C., et al. (2011). Identification and surveillance of 19 lynch syndrome families in southern italy: Report of six novel germline mutations and a common founder mutation. *Familial Cancer, 10*(2), 285-295.

Lea, D. H. (1996). Emerging quality improvement measures in genetic counseling. *Journal of Genetic Counseling, 5*(3), 123-137.

Lehmann, L. S., Weeks, J. C., Klar, N., Biener, L., & Garber, J. E. (2000). Disclosure of familial genetic information: Perceptions of the duty to inform. *The American Journal of Medicine, 109*(9), 705-711.

Lerman, C., Hughes, C., Trock, B. J., Myers, R. E., Main, D., Bonney, A., et al. (1999). Genetic testing in families with hereditary nonpolyposis colon cancer. *The Journal of the American Medical Association, 281*(17), 1618-1622.

Lerman, C., Marshall, J., Audrain, J., & Gomez-Caminero, A. (1996). Genetic testing for colon cancer susceptibility: Anticipated reactions of patients and challenges to providers. *International Journal of Cancer, 69*(1), 58-61.

Lerman, C., Trock, B., Rimer, B. K., Boyce, A., Jepson, C., & Engstrom, P. F. (1991a). Psychological and behavioral implications of abnormal mammograms. *Annals of Internal Medicine, 114*(8), 657-661.

Lerman, C., Trock, B., Rimer, B. K., Jepson, C., Brody, D., & Boyce, A. (1991b). Psychological side effects of breast cancer screening. *Health Psychology, 10*(4), 259-267.

Levin, B. (1996). Screening for colorectal cancer. *Cancer Control: Journal of the Moffitt Cancer Center, 3*(1), 20-25.

Liljegren, A., Lindgren, G., Brandberg, Y., Rotstein, S., Nilsson, B., Hatschek, T., et al. (2004). Individuals with an increased risk of colorectal cancer: Perceived benefits and psychological aspects of surveillance by means of regular colonoscopies. *Journal of Clinical Oncology, 22*(9), 1736-1742.

Lin, K. M., Shashidharan, M., Thorson, A. G., Ternent, C. A., Blatchford, G. J., Christensen, M. A., et al. (1998). Cumulative incidence of colorectal and extracolonic cancers in MLH1 and MSH2 mutation carriers of hereditary nonpolyposis colorectal cancer. *Journal of Gastrointestinal Surgery, 2*(1), 67-71.

Lincoln, Y.S., & Guba, E.G. (1985). *Naturalistic inquiry*. California: Sage.

Lindblom, A., Tannergard, P., Werelius, B., & Nordenskjold, M. (1993). Genetic mapping of a second locus predisposing to hereditary non-polyposis colon cancer. *Nature Genetics, 5*(3), 279-282.

Lindor, N. M., Burgart, L. J., Leontovich, O., Goldberg, R. M., Cunningham, J. M., Sargent, D. J., et al. (2002). Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. *Journal of Clinical Oncology, 20*(4), 1043-1048.

Lindor, N. M., Petersen, G. M., Hadley, D. W., Kinney, A. Y., Miesfeldt, S., Lu, K. H., et al. (2006). Recommendations for the care of individuals with an inherited predisposition to lynch syndrome: A systematic review. *The Journal of the American Medical Association, 296*(12), 1507-1517.

Liu, B., Parsons, R. E., Hamilton, S. R., Petersen, G. M., Lynch, H. T., Watson, P., et al. (1994). hMSH2 mutations in hereditary nonpolyposis colorectal cancer kindreds. *Cancer Research, 54*(17), 4590-4594.

Liu, S. R., Zhao, B., Wang, Z. J., Wan, Y. L., & Huang, Y. T. (2004). Clinical features and mismatch repair gene mutation screening in chinese patients with hereditary nonpolyposis colorectal carcinoma. *World Journal of Gastroenterology, 10*(18), 2647-2651.

Lodder, L. N., Frets, P. G., Trijsburg, R. W., Meijers-Heijboer, E. J., Klijn, J. G., Duivenvoorden, H. J., et al. (1999). Presymptomatic testing for BRCA1 and BRCA2: How distressing are the pre-test weeks? *Journal of Medical Genetics, 36*(12), 906-913.

Lynch, H. T., & de la Chapelle, A. (1999). Genetic susceptibility to non-polyposis colorectal cancer. *British Medical Journal, 36*(11), 801-818.

Lynch, H. T., & de la Chapelle, A. (2003). Hereditary colorectal cancer. *The New England Journal of Medicine, 348*(10), 919-932.

Lynch, H. T., Fusaro, R. M., Lynch, J. F., & Brand, R. (2008). Pancreatic cancer and the FAMMM syndrome. *Familial Cancer, 7*(1), 103-112.

Lynch, H. T., Fusaro, R. M., Roberts, L., Voorhees, G. J., & Lynch, J. F. (1985a). Muir-torre syndrome in several members of a family with a variant of the cancer family syndrome. *The British Journal of Dermatology, 113*(3), 295-301.

Lynch, H. T., & Krush, A. J. (1971). Cancer family "G" revisited: 1895-1970. *Cancer, 27*(6), 1505-1511.

Lynch, H. T., & Lynch, J. F. (2000). Hereditary nonpolyposis colorectal cancer. *Seminars in Surgical Oncology, 18*(4), 305-313.

Lynch, H. T., & Lynch, J. F. (2000). Hereditary nonpolyposis colorectal cancer. *Seminars in Surgical Oncology, 18*(4), 305-313.

Lynch, H. T., Lynch, P. M., Lanspa, S. J., Snyder, C. L., Lynch, J. F., & Boland, C. R. (2009). Review of the lynch syndrome: History, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. *Clinical Genetics, 76*(1), 1-18.

Lynch, H. T., Lynch, P. M., Pester, J., & Fusaro, R. M. (1981). The cancer family syndrome: Rare cutaneous phenotypic linkage of torre's syndrome. *Archives of Internal Medicine, 141*(5), 607-611.

Lynch, H. T., Richardson, J. D., Amin, M., Lynch, J. F., Cavalieri, R. J., Bronson, E., et al. (1991). Variable gastrointestinal and urologic cancers in a lynch syndrome II kindred. *Diseases of the Colon and Rectum, 34*(10), 891-895.

Lynch, H. T., Shaw, M. W., Magnuson, C. W., Larsen, A. L., & Krush, A. J. (1966). Hereditary factors in cancer. study of two large midwestern kindreds. *Archives of Internal Medicine, 117*(2), 206-212.

Lynch, H. T., & Smyrk, T. (1996). Hereditary nonpolyposis colorectal cancer (lynch syndrome). An updated review. *Cancer, 78*(6), 1149-1167.

Lynch, H. T., Smyrk, T., & Lynch, J. F. (1998). Molecular genetics and clinical-pathology features of hereditary nonpolyposis colorectal carcinoma (lynch syndrome): Historical journey from pedigree anecdote to molecular genetic confirmation. *Oncology, 55*(2), 103-108.

Lynch, H. T., Smyrk, T. C., Lanspa, S. J., Jenkins, J. X., Cavalieri, J., & Lynch, J. F. (1993a). Cancer control problems in the lynch syndromes. *Diseases of the Colon and Rectum, 36*(3), 254-260.

Lynch, H. T., Smyrk, T. C., Watson, P., Lanspa, S. J., Lynch, J. F., Lynch, P. M., et al. (1993b). Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: An updated review. *Gastroenterology, 104*(5), 1535-1549.

Lynch, H. T., Voorhees, G. J., Lanspa, S. J., McGreevy, P. S., & Lynch, J. F. (1985b). Pancreatic carcinoma and hereditary nonpolyposis colorectal cancer: A family study. *British Journal of Cancer, 52*(2), 271-273.

Mack, L. A., Cook, L. S., Temple, W. J., Carlson, L. E., Hilsden, R. J., & Paolucci, E. O. (2009). Colorectal cancer screening among first-degree relatives of

colorectal cancer patients: Benefits and barriers. *Annals of Surgical Oncology, 16*(8), 2092-2100.

Marcus, M. & Minc, H. (1988). *Introduction to linear algebra*. New York: Dover.

Marshall, M., Lockwood, A., Bradley, C., Adams, C., Joy, C., & Fenton, M. (2000). Unpublished rating scales: A major source of bias in randomised controlled trials of treatments for schizophrenia. *The British Journal of Psychiatry, 176*, 249-252.

Marshall, C. & Rossman, G.B. (1999). Designing qualitative research (3rd Edn). California: Sage.

Maxwell, A. E., Bastani, R., & Warda, U. S. (2000). Demographic predictors of cancer screening among filipino and korean immigrants in the united states. *American Journal of Preventive Medicine, 18*(1), 62-68.

Mcallister, M. (2002). Predictive genetic testing and beyond: A theory of engagement. *Journal of Health Psychology, 7*(5), 491-508.

McAllister, M. (2003). Personal theories of inheritance, coping strategies, risk perception and engagement in hereditary non-polyposis colon cancer families offered genetic testing. *Clinical Genetics, 64*(3), 179-189.

McCaffery, K., Wardle, J., & Waller, J. (2003). Knowledge, attitudes, and behavioral intentions in relation to the early detection of colorectal cancer in the united kingdom. *Preventive Medicine, 36*(5), 525-535.

McCann, S., Macauley, D., Barnett, Y., Bunting, B., Bradley, A., Jeffers, L., et al. (2009). Family communication, genetic testing and colonoscopy screening in hereditary non-polyposis colon cancer: A qualitative study. *Psycho-Oncology,* 18(11), 1208-1215.

McCarthy, B. D., & Moskowitz, M. A. (1993). Screening flexible sigmoidoscopy: Patient attitudes and compliance. *Journal of General Internal Medicine, 8*(3), 120-125.

McIntyre, M. T., Nkosi, M., Mutyambizi, V., Castillo-Riquelme, M., Gilson, L., Erasmus, E., et al. (2007). Shield work package 1 report. Retrieved June 2010 from www.web.uct.ac.za/depts/heu/SHIELD/reports/SouthAfrica1.pdf.

Mcintyre, D., Thiede, M., Nkosi, M. et al. (2007). *A critical analysis of the current South African health system*. Cape Town: Health Economics unit, University

of Cape Town and the Centre for Health Policy, University of the Witwatersrand.

McMichael, A., McCall, M., Hartshore, J., & Woodings, T. (1980). Patterns of gastro-intestinal cancer in european migrants to australia: The role of dietary change. *International Journal of Cancer, 25*(4), 431-437.

McMillan, J.H. & Schumacher, S. (2001). *Research in education: A conceptual introduction* (5th Edn). New York: Longman.

Mecklin, J. P. (1987). Frequency of hereditary colorectal carcinoma. *Gastroenterology, 93*(5), 1021-1025.

Mecklin, J. P., Jarvinen, H. J., Hakkiluoto, A., Hallikas, H., Hiltunen, K. M., Harkonen, N., et al. (1995). Frequency of hereditary nonpolyposis colorectal cancer. A prospective multicenter study in finland. *Diseases of the Colon and Rectum, 38*(6), 588-593.

Mecklin, J. P., Jarvinen, H. J., & Peltokallio, P. (1986). Cancer family syndrome. Genetic analysis of 22 finnish kindreds. *Gastroenterology, 90*(2), 328-333.

Mecklin, J. P., Jarvinen, H. J., & Virolainen, M. (1992). The association between cholangiocarcinoma and hereditary nonpolyposis colorectal carcinoma. *Cancer, 69*(5), 1112-1114.

Mecklin, J. P., & Ponz de Leon, M. (1994). Epidemiology of HNPCC. *Anticancer Research, 14*(4B), 1625-1629.

Meiser, B., Collins, V., Warren, R., Gaff, C., St John, D. J., Young, M. A., et al. (2004). Psychological impact of genetic testing for hereditary non-polyposis colorectal cancer. *Clinical Genetics, 66*(6), 502-511.

Mesters, I., Ausems, M., Eichhorn, S., & Vasen, H. (2005). Informing one's family about genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): A retrospective exploratory study. *Familial Cancer, 4*(2), 163-167.

Michels, K. B., Fuchs, C. S., Giovannucci, E., Colditz, G. A., Hunter, D. J., Stampfer, M. J., et al. (2005). Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. *Cancer Epidemiology Biomarkers & Prevention, 14*(4), 842-849.

Michie, S., McDonald, V., & Marteau, T. M. (1997). Genetic counselling: Information given, recall and satisfaction. *Patient Education and Counseling, 32*(1-2), 101-106.

Minichiello, V., Aroni, R., Timewell, E., Alexander, L. (1990). *In depth-interviewing: Researching people*. Melbourne: Longman Cheshire.

Miyaki, M., Konishi, M., Tanaka, K., Kikuchi-Yanoshita, R., Muraoka, M., Yasuno, M., et al. (1997). Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. *Nature Genetics, 17*(3), 271-272.

Modica, S., Roncucci, L., Benatti, P., Gafa, L., Tamassia, M. G., Dardanoni, L., et al. (1995). Familial aggregation of tumors and detection of hereditary non-polyposis colorectal cancer in 3-year experience of 2 population-based colorectal-cancer registries. *International Journal of Cancer, 62*(6), 685-690.

Moisio, A. L., Sistonen, P., Weissenbach, J., de la Chapelle, A., & Peltomaki, P. (1996). Age and origin of two common MLH1 mutations predisposing to hereditary colon cancer. *American Journal of Human Genetics, 59*(6), 1243-1251.

Mooney, G. H., & McIntyre, D. E. (2008). South africa: A 21st century apartheid in health and health care? *The Medical Journal of Australia, 189*(11-12), 637-640.

Morse, J. M. (1992). *Qualitative health research*. Newbury Park, California: Sage.

Morse, J. M. (1994). *Critical issues in qualitative research methods*. Thousand Oaks, California: Sage.

Mqoqi, N. (2004). *Incidence of histologically diagnosed cancer in south africa, 1998-1999* National Cancer Registry of South Africa. South Africa: National Health Laboratory Service.

Mukherjee, B., Rennert, G., Ahn, J., Dishon, S., Lejbkowicz, F., Rennert, H. S., et al. (2011). High risk of colorectal and endometrial cancer in ashkenazi families with the MSH2 A636P founder mutation. *Gastroenterology, 140*(7), 1919-1926.

Murakami, Y., Okamura, H., Sugano, K., Yoshida, T., Kazuma, K., Akechi, T., et al. (2004). Psychologic distress after disclosure of genetic test results regarding hereditary nonpolyposis colorectal carcinoma. *Cancer, 101*(2), 395-403.

Myers, R. E., Trock, B. J., Lerman, C., Wolf, T., Ross, E., & Engstrom, P. F. (1990). Adherence to colorectal cancer screening in an HMO population. *Preventive Medicine, 19*(5), 502-514.

Natale-Pereira, A., Marks, J., Vega, M., Mouzon, D., Hudson, S. V., & Salas-Lopez, D. (2008). Barriers and facilitators for colorectal cancer screening practices in the latino community: Perspectives from community leaders. *Cancer Control, 15*(2), 157-165.

Natarajan, N., Watson, P., Silva-Lopez, E., & Lynch, H. T. (2010). Comparison of extended colectomy and limited resection in patients with lynch syndrome. *Diseases of the Colon and Rectum, 53*(1), 77-82.

National Cancer Registry. (1999). *Lifetime Risk for five leading cancers in adults by population group and sex*. Retrieved April 2010 from http://www.cansa.org.za/cgi-bin/giga.cgi?cmd=cause_dir_news_item&cause_id=1056&news_id=31937&cat_id=746.

National Consultative Ethics Committee for Health and Life Sciences. (2003). *Regarding the Obligation to Disclose Genetic Information of Concern to the Family in the Event of Medical Necessity*. France: National Consultative Ethics Committee for Health and Life Sciences.

National Research Council. (1982). *Commitee on diet, nutrition and cancer*. Washington, DC: National Academy Press.

National Society of Genetic Counselors' Definition Task Force, Resta, R., Biesecker, B. B., Bennett, R. L., Blum, S., Hahn, S. E., et al. (2006). A new definition of genetic counseling: National society of genetic counselors' task force report. *Journal of Genetic Counseling, 15*(2), 77-83.

Naussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson and Thompson: Genetics in medicine* (6th Edn). New York: W.B. Saunders Company.

Neuhausen, S. L. (2000). Founder populations and their uses for breast cancer genetics. *Breast Cancer Research, 2*(2), 77-81.

Neville, C. (2007). *The complete guide to referencing and avoiding plagiarism*. New York: Open University Press McGrawHill.

Newcomb, P. A., Baron, J., Cotterchio, M., Gallinger, S., Grove, J., Haile, R., et al. (2007). Colon cancer family registry: An international resource for studies of the genetic epidemiology of colon cancer. *Cancer Epidemiology, Biomarkers & Prevention, 16*(11), 2331-2343.

Nordin, K., Liden, A., Hansson, M., Rosenquist, R., & Berglund, G. (2002). Coping style, psychological distress, risk perception, and satisfaction in subjects

attending genetic counselling for hereditary cancer. *Journal of Medical Genetics, 39*(9), 689-694.

Northam, A. (2010). *Colorectal cancer: A neuropsychological approach to non-adherence screening guidelines of individuals with Lynch syndrome in the Western Cape*. Master's thesis. University of Cape Town, South Africa.

Nystrom-Lahti, M., Sistonen, P., Mecklin, J. P., Pylkkanen, L., Aaltonen, L. A., Jarvinen, H., et al. (1994). Close linkage to chromosome 3p and conservation of ancestral founding haplotype in hereditary nonpolyposis colorectal cancer families. *Proceedings of the National Academy of Sciences of the United States of America, 91*(13), 6054-6058.

Offit, K., Kohut, K., Clagett, B., Wadsworth, E. A., Lafaro, K. J., Cummings, S., et al. (2006). Cancer genetic testing and assisted reproduction. *Journal of Clinical Oncology, 24*(29), 4775-4782.

Ondrusek, N., Warner, E., & Goel, V. (1999). Development of a knowledge scale about breast cancer and heredity (BCHK). *Breast Cancer Research and Treatment, 53*(1), 69-75.

Pande, M., Lynch, P. M., Hopper, J. L., Jenkins, M. A., Gallinger, S., Haile, R. W., et al. (2010). Smoking and colorectal cancer in lynch syndrome: Results from the colon cancer family registry and the university of texas MD anderson cancer center. *Clinical Cancer Research, 16*(4), 1331-1339.

Parc, Y., Boisson, C., Thomas, G., & Olschwang, S. (2003). Cancer risk in 348 french MSH2 or MLH1 gene carriers. *Journal of Medical Genetics, 40*(3), 208-213.

Park, J. G., Kim, D. W., Hong, C. W., Nam, B. H., Shin, Y. K., Hong, S. H., et al. (2006). Germ line mutations of mismatch repair genes in hereditary nonpolyposis colorectal cancer patients with small bowel cancer: International society for gastrointestinal hereditary tumours collaborative study. *Clinical Cancer Research, 12*(11 Pt 1), 3389-3393.

Park, Y. J., Shin, K. H., & Park, J. G. (2000). Risk of gastric cancer in hereditary nonpolyposis colorectal cancer in korea. *Clinical Cancer Research, 6*(8), 2994-2998.

Parkerson, G. R.,Jr, & Broadhead, W. E. (1997). Screening for anxiety and depression in primary care with the duke anxiety-depression scale. *Family Medicine, 29*(3), 177-181.

Parkerson, G. R.,Jr, Broadhead, W. E., & Tse, C. K. (1990). The duke health profile. A 17-item measure of health and dysfunction. *Medical Care, 28*(11), 1056-1072.

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics, 2002. *A Cancer Journal for Clinicians, 55*(2), 74-108.

Parrott, S., & DelVecchio, M. (2007). *Professional Status Survey 2006. National Society of Genetic Counselors, Inc.* Retrieved May 2010 from www.nsgc.org/client_files/careers/2006_PSS_Results.doc.

Patenaude, A. F., Dorval, M., DiGianni, L. S., Schneider, K. A., Chittenden, A., & Garber, J. E. (2006). Sharing BRCA1/2 test results with first-degree relatives: Factors predicting who women tell. *Journal of Clinical Oncology, 24*(4), 700-706.

Patton, M.Q. (2002). *Qualitative research and evaluation methods* (3rd Edn). London: Sage.

Payne, K., Nicholls, S., McAllister, M., Macleod, R., Donnai, D., & Davies, L. M. (2008). Outcome measurement in clinical genetics services: A systematic review of validated measures. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 11*(3), 497-508.

Peel, D. J., Ziogas, A., Fox, E. A., Gildea, M., Laham, B., Clements, E., et al. (2000). Characterization of hereditary nonpolyposis colorectal cancer families from a population-based series of cases. *Journal of the National Cancer Institute, 92*(18), 1517-1522.

Peltomaki, P. (2003). Role of DNA mismatch repair defects in the pathogenesis of human cancer. *Journal of Clinical Oncology, 21*(6), 1174-1179.

Peltomaki, P., Aaltonen, L. A., Sistonen, P., Pylkkanen, L., Mecklin, J. P., Jarvinen, H., et al. (1993). Genetic mapping of a locus predisposing to human colorectal cancer. *Science, 260*(5109), 810-812.

Peters, J. A., & Biesecker, B. B. (1997). Genetic counselling and hereditary cancer. *Cancer, 80*(S3), 576-586.

Peterson, S. K., Watts, B. G., Koehly, L. M., Vernon, S. W., Baile, W. F., Kohlmann, W. K., et al. (2003). How families communicate about HNPCC genetic testing: Findings from a qualitative study. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 119C*(1), 78-86.

Pieterse, A. H., van Dulmen, A. M., Beemer, F. A., Bensing, J. M., & Ausems, M. G. (2007). Cancer genetic counseling: Communication and counselees' post-visit satisfaction, cognitions, anxiety, and needs fulfillment. *Journal of Genetic Counseling, 16*(1), 85-96.

Pilnick, A., & Dingwall, R. (2001). Research directions in genetic counselling: A review of the literature. *Patient Education and Counseling, 44*(2), 95-105.

Plaschke, J., Engel, C., Kruger, S., Holinski-Feder, E., Pagenstecher, C., Mangold, E., et al. (2004). Lower incidence of colorectal cancer and later age of disease onset in 27 families with pathogenic MSH6 germline mutations compared with families with MLH1 or MSH2 mutations: The german hereditary nonpolyposis colorectal cancer consortium. *Journal of Clinical Oncology, 22*(22), 4486-4494.

Ponti, G., & Ponz de Leon, M. (2005). Muir-torre syndrome. *The Lancet Oncology, 6*(12), 980-987.

Ponz de Leon, M., Benatti, P., Percesepe, A., Di Gregorio, C., Fante, R., Losi, L., et al. (1999). Epidemiology of cancer of the large bowel-the 12-year experience of a specialized registry in northern italy. *Italian Journal of Gastroenterology and Hepatology, 31*(1), 10-18.

Ponz de Leon, M., Sassatelli, R., Benatti, P., & Roncucci, L. (1993). Identification of hereditary nonpolyposis colorectal cancer in the general population. The 6-year experience of a population-based registry. *Cancer, 71*(11), 3493-3501.

Ponz de Leon, M., Sassatelli, R., Sacchetti, C., Zanghieri, G., Scalmati, A., & Roncucci, L. (1989). Familial aggregation of tumors in the three-year experience of a population-based colorectal cancer registry. *Cancer Research, 49*(15), 4344-4348.

Pope, C., Ziebland, S., & Mays, N. (2000). Qualitative research in health care. Analysing qualitative data. *British Medical Journal, 320*(7227), 114-116.

Pope, C. & Mays, N. (2000). Qualitative methods in health research. In: C. Pope, N. Mays (Ed). *Qualitative research in Health Care* (2nd Edn). London: BMJ Books.

Poulton, B. C. (1996). Use of the consultation satisfaction questionnaire to examine patients' satisfaction with general practitioners and community nurses: Reliability, replicability and discriminant validity. *The British Journal of General Practice, 46*(402), 26-31.

Powe, B. D. (1995). Fatalism among elderly african americans. effects on colorectal cancer screening. *Cancer Nursing, 18*(5), 385-392.

President's Commission. (1983). *Screening and Counselling for Genetic Conditions. The ethical, social, and legal implications of genetic screening, counselling, and education programs*. Washington, DC: US.GPO.

Price, J. H. (1993). Perceptions of colorectal cancer in a socioeconomically disadvantaged population. *Journal of Community Health, 18*(6), 347-362.

Prucka, S. K., McIlvried, D. E., & Korf, B. R. (2008). Cancer risk assessment and the genetic counseling process: Using hereditary breast and ovarian cancer as an example. *Medical Principles and Practice, 17*(3), 173-189.

Pylvanainen, K., Kairaluoma, M., & Mecklin, J. P. (2006). Compliance and satisfaction with long-term surveillance in finnish HNPCC families. *Familial Cancer, 5*(2), 175-178.

Quehenberger, F., Vasen, H. F., & van Houwelingen, H. C. (2005). Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: Correction for ascertainment. *Journal of Medical Genetics, 42*(6), 491-496.

Ramesar, R. S., Madden, M. V., Felix, R., Harocopos, C. J., Westbrook, C. A., Jones, G., et al. (2000). Molecular genetics improves the management of hereditary non-polyposis colorectal cancer. *South African Medical Journal, 90*(7), 709-714.

Ramsoekh, D., Wagner, A., van Leerdam, M. E., Dooijes, D., Tops, C. M., Steyerberg, E. W., et al. (2009). Cancer risk in MLH1, MSH2 and MSH6 mutation carriers; different risk profiles may influence clinical management. [Electronic version]. *Hereditary Cancer in Clinical Practice, 7*(1), 17. [Retrieved April 2010 from PubMed Online database].

Rankhumise, E., Netswera, G., & Meyer, M. (2001). Employees' perceptions of the implementation of affirmative action in the health sector in the standerton district in south africa. *Curationis, 24*(4), 52-58.

Ravnik-Glavac, M., Potocnik, U., & Glavac, D. (2000). Incidence of germline hMLH1 and hMSH2 mutations (HNPCC patients) among newly diagnosed colorectal cancers in a slovenian population. *British Medical Journal, 37*(7), 533-536.

Raymond, V. M., & Everett, J. N. (2009). Genetic counselling and genetic testing in hereditary gastrointestinal cancer syndromes. *Best Practice & Research.Clinical Gastroenterology, 23*(2), 275-283.

Research ethics and environmental health. (2002): *Conference 2003 'dialogues for improving research ethics in environmental and public health'*. Retrieved September 2009 from http://www.researchethics.org/conference2.pdf.

Read, A. & Donnai, D. (2007). *New clinical genetics*. Oxford: Scion Publishing.

Rees, G., Martin, P. R., & Macrae, F. A. (2008). Screening participation in individuals with a family history of colorectal cancer: A review. *European Journal of Cancer Care, 17*(3), 221-232.

Renkonen-Sinisalo, L., Butzow, R., Leminen, A., Lehtovirta, P., Mecklin, J. P., & Jarvinen, H. J. (2007). Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *International Journal of Cancer, 120*(4), 821-824.

Resnick, K. E., Hampel, H., Fishel, R., & Cohn, D. E. (2009). Current and emerging trends in lynch syndrome identification in women with endometrial cancer. *Gynecologic Oncology, 114*(1), 128-134.

Resta, R. G. (2006). Defining and redefining the scope and goals of genetic counseling. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 142C*(4), 269-275.

Ribic, C. M., Sargent, D. J., Moore, M. J., Thibodeau, S. N., French, A. J., Goldberg, R. M., et al. (2003). Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *The New England Journal of Medicine, 349*(3), 247-257.

Richards, M. (1996). Families, kinship and genetics. In: T. Marteau and M. Richards (Ed). The *Troubled Helix: Social and Psychological Implications of the New Human Genetics,* 249-273. Cambridge: Cambridge University Press.

Richardson, J. L., Danley, K., Mondrus, G. T., Deapen, D., & Mack, T. (1995). Adherence to screening examinations for colorectal cancer after diagnosis in a first-degree relative. *Preventive Medicine, 24*(2), 166-170.

Riegler, G., Savastano, A., Selvaggi, F., Ciociano, R., Martino, R., Riccio, G., et al. (1999). Prevalence of HNPCC in a series of consecutive patients on the first endoscopic diagnosis of colorectal cancer: A multicenter study. The italian collaborative group. *Endoscopy, 31*(5), 337-341.

Risinger, J. I., Barrett, J. C., Watson, P., Lynch, H. T., & Boyd, J. (1996). Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. *Cancer, 77*(9), 1836-1843.

Rodriguez-Bigas, M. A., Boland, C. R., Hamilton, S. R., Henson, D. E., Jass, J. R., Khan, P. M., et al. (1997). A national cancer institute workshop on hereditary nonpolyposis colorectal cancer syndrome: Meeting highlights and bethesda guidelines. *Journal of the National Cancer Institute, 89*(23), 1758-1762.

Rodriguez-Bigas, M. A., Vasen, H. F., Lynch, H. T., Watson, P., Myrhoj, T., Jarvinen, H. J., et al. (1998). Characteristics of small bowel carcinoma in hereditary nonpolyposis colorectal carcinoma. international collaborative group on HNPCC. *Cancer, 83*(2), 240-244.

Rossouw, D. (2003). *Intellectual tools: Skills for the human sciences* (2nd Edn). Cape Town: Van Schaik.

Rubin, R. B., Perse, E. M., & Barbato, C. A. (1988). Conceptualization and measurement of interpersonal communication motives. *Human Communication Research, 14*(4), 602-628.

Ruppelt, T. (2011). Personal communication with Theresa Ruppelt [National Health Laboratory Services, South Africa].

Sagi, M., Kaduri, L., Zlotogora, J., & Peretz, T. (1998). The effect of genetic counseling on knowledge and perceptions regarding risks for breast cancer. *Journal of Genetic Counseling, 7*(5), 417-434.

Salovaara, R., Loukola, A., Kristo, P., Kaariainen, H., Ahtola, H., Eskelinen, M., et al. (2000). Population-based molecular detection of hereditary nonpolyposis colorectal cancer. *Journal of Clinical Oncology, 18*(11), 2193-2200.

Samowitz, W. S., Curtin, K., Lin, H. H., Robertson, M. A., Schaffer, D., Nichols, M., et al. (2001). The colon cancer burden of genetically defined hereditary nonpolyposis colon cancer. *Gastroenterology, 121*(4), 830-838.

Sankila, R., Aaltonen, L. A., Jarvinen, H. J., & Mecklin, J. P. (1996). Better survival rates in patients with MLH1-associated hereditary colorectal cancer. *Gastroenterology, 110*(3), 682-687.

Sarantakos, S. (1993). *Social Research*. Melbourne: Macmillan Press Ltd.

Savanhu, T.K. (2005). *Haplotyping and estimating the age of the founder mutation identifying familial colorectal cancer.* Bachelor of Science thesis. University of Cape Town, South Africa.

Schmeler, K. M., Lynch, H. T., Chen, L. M., Munsell, M. F., Soliman, P. T., Clark, M. B., et al. (2006). Prophylactic surgery to reduce the risk of gynecologic cancers in the lynch syndrome. *The New England Journal of Medicine, 354*(3), 261-269.

Schneider, K. A., Chittenden, A. B., Branda, K. J., Keenan, M. A., Joffe, S., Patenaude, A. F., et al. (2006). Ethical issues in cancer genetics: Whose information is it? *Journal of Genetic Counseling, 15*(6), 491-503.

Schulmann, K., Reiser, M., & Schmiegel, W. (2002). Colonic cancer and polyps. *Best Practice & Research Clinical Gastroenterology, 16*(1), 91-114.

Schulmann, K., Brasch, F. E., Kunstmann, E., Engel, C., Pagenstecher, C., Vogelsang, H., et al. (2005). HNPCC-associated small bowel cancer: Clinical and molecular characteristics. *Gastroenterology, 128*(3), 590-599.

Schulmann, K., Engel, C., Propping, P., & Schmiegel, W. (2008). Small bowel cancer risk in lynch syndrome. *Gut, 57*(11), 1629-1630.

Scott, R. J., McPhillips, M., Meldrum, C. J., Fitzgerald, P. E., Adams, K., Spigelman, A. D., et al. (2001). Hereditary nonpolyposis colorectal cancer in 95 families: Differences and similarities between mutation-positive and mutation-negative kindreds. *American Journal of Human Genetics, 68*(1), 118-127.

Segal, J., Esplen, M. J., Toner, B., Baedorf, S., Narod, S., & Butler, K. (2004). An investigation of the disclosure process and support needs of BRCA1 and BRCA2 carriers. *American Journal of Medical Genetics. Part A, 125A*(3), 267-272.

Shiloh, S. (1996). Decision-making in the context of genetic risk. In: T. Marteau, M. Richards (Ed). *The troubled helix. The social and psychological implications of the new human genetics*. Cambridge: Cambridge University Press.

Shiloh, S., Avdor, O., & Goodman, R. M. (1990). Satisfaction with genetic counseling: Dimensions and measurement. *American Journal of Medical Genetics, 37*(4), 522-529.

Shiloh, S., & Saxe, L. (1989). Perception of recurrence risks by genetic counselees. *Psychology and Health*, 3, 45-61.

Shiloh, S., Koehly, L., Jenkins, J., Martin, J., & Hadley, D. (2008). Monitoring coping style moderates emotional reactions to genetic testing for hereditary nonpolyposis colorectal cancer: A longitudinal study. *Psycho-Oncology, 17*(8), 746-755.

Sitas, F., Madhoo, J., & Wessie, J. (1998). *Incidence of histologically diagnosed cancer in south africa, 1993-1995*. Johannesburg: National Cancer Registry of South African Institute Medical Research.

Smyrk, T. C., Lynch, H. T., Watson, P. A., & Appelman, H. D. (1990). Histologic features of hereditary nonpolyposis colorectal carcinoma. In: J. Utsunomiya and H.T. Lynch (Ed). *Hereditary Colorectal Cancer, 357-362.* Tokyo: Springer-Verlag.

South, C. D., Hampel, H., Comeras, I., Westman, J. A., Frankel, W. L., & de la Chapelle, A. (2008). The frequency of muir-torre syndrome among lynch syndrome families. *Journal of the National Cancer Institute, 100*(4), 277-281.

South African Health Review (2006). *Health systems trust*. Retrieved March 2010 from http://www.hst.org.za/publications/item.php?item_id=697.

South Africa Government. (2008). *Minister of social development Zola Skweyiya announces increases on social grants*. Retrieved April 2010 from http://www.dsd.gov.za/index.php?option=com_content&task=view&id=79&Itemid=106.

South African Government Services: (2010). *Child grants and older person grants 2010.* Retrieved May 2010 from http://www.services.gov.za/servicesforpeople/Socialbenefits/oldagegrant.aspx?Language=en-ZA.

SPSS Inc. (2001). *Statistical package for the social sciences*. Chicago: SPSS Inc.

Stanley, A. J., Gaff, C. L., Aittomaki, A. K., Fabre, L. C., Macrae, F. A., & St John, J. (2000). Value of predictive genetic testing in management of hereditary non-polyposis colorectal cancer (HNPCC). *The Medical Journal of Australia, 172*(7), 313-316.

Starks, H., & Trinidad, B. (2007). Choose your method: A comparison of phenomenology, discourse analysis, and grounded theory. *Qualitative Health Research, 17*(10), 1372-1380.

American society of clinical oncology:.(1996). Genetic testing for cancer susceptibility, adopted on february 20, 1996. *Journal of Clinical Oncology, 14*(5), 1730-1736.

Statistics South Africa. (2005). *National 2001 census*. Retrieved March 2010 from http://www.statssa.gov.za/.

Stella, A., Surdo, N. C., Lastella, P., Barana, D., Oliani, C., Tibiletti, M. G., et al. (2007). Germline novel MSH2 deletions and a founder MSH2 deletion associated with anticipation effects in HNPCC. *Clinical Genetics, 71*(2), 130-139.

Stephenson, B. M., Murday, V. A., Finan, P. J., Quirke, P., Dixon, M. F., & Bishop, D. T. (1993). Feasibility of family based screening for colorectal neoplasia: Experience in one general surgical practice. *Gut, 34*(1), 96-100.

Steyn, K., & Bradshaw, D. (2001). Non-communicable disease surveillance in developing countries. *Scandinavian Journal of Public Health, 29*(3), 161-165.

Stoffel, E. M., Ford, B., Mercado, R. C., Punglia, D., Kohlmann, W., Conrad, P., et al. (2008). Sharing genetic test results in lynch syndrome: Communication with close and distant relatives. *Clinical Gastroenterology and Hepatology, 6*(3), 333-338.

Stoffel, E. M., Garber, J. E., Grover, S., Russo, L., Johnson, J., & Syngal, S. (2003). Cancer surveillance is often inadequate in people at high risk for colorectal cancer [Electronic version]. *Journal of Medical Genetics, 40*(5), e54. [Retrieved August 2010 from PubMed Online database].

Stoffel, E. M., Mercado, R. C., Kohlmann, W., Ford, B., Grover, S., Conrad, P., et al. (2010). Prevalence and predictors of appropriate colorectal cancer surveillance in lynch syndrome. *The American Journal of Gastroenterology, 105*(8), 1851-1860.

Stormorken, A. T., Clark, N., Grindedal, E., Maehle, L., & Moller, P. (2007). Prevention of colorectal cancer by colonoscopic surveillance in families with hereditary colorectal cancer. *Scandinavian Journal of Gastroenterology, 42*(5), 611-617.

Strate, L. L., & Syngal, S. (2005). Hereditary colorectal cancer syndromes. *Cancer Causes & Control, 16*(3), 201-213.

Street, E.C., & Soldan, J. (1998). A conceptual framework for the psychosocial issues faced by families with genetic conditions. *Families Systems and Health*, 16, 217-231.

Stupart, D. A., Goldberg, P. A., Algar, U., & Ramesar, R. (2009a). Cancer risk in a cohort of subjects carrying a single mismatch repair gene mutation. *Familial Cancer, 8(4), 519-523.*

Stupart, D. A., Goldberg, P. A., Algar, U., & Ramesar, R. (2009b). Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. *Colorectal Disease, 11*(2), 126-130.

Subramanian, S., Klosterman, M., Amonkar, M. M., & Hunt, T. L. (2004). Adherence with colorectal cancer screening guidelines: A review. *Preventive Medicine, 38*(5), 536-550.

Sun, W. Y., Basch, C. E., Wolf, R. L., & Li, X. J. (2004). Factors associated with colorectal cancer screening among chinese-americans. *Preventive Medicine, 39*(2), 323-329.

Suthers, G. K., Armstrong, J., McCormack, J., & Trott, D. (2006). Letting the family know: Balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *Journal of Medical Genetics, 43*(8), 665-670.

Syngal, S., Fox, E. A., Eng, C., Kolodner, R. D., & Garber, J. E. (2000). Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. *Journal of Medical Genetics, 37*(9), 641-645.

Tait, N., Joubert, J., Whiteford, A., van Zyl, J., Krige, D., & Pillay, B. (1996). *A socio-economic atlas of south africa: A demographic, socio-economic and cultural profile of South Africa.* Pretoria: HSRC Press.

Taitz, J. (1990). The rule of medical confidentiality v. the moral duty to warn an endangered third party. *South African Medical Journal, 78*(1), 29-33.

Talseth-Palmer, B. A., McPhillips, M., Groombridge, C., Spigelman, A., & Scott, R. J. (2010). MSH6 and PMS2 mutation positive australian lynch syndrome families: Novel mutations, cancer risk and age of diagnosis of colorectal cancer. [Electronic version]. *Hereditary Cancer in Clinical Practice, 8*(1), 5. [Retrieved January 2011 from BioMed Central Online database].

Tanyi, M. (2009). Our experience with the incidence of hereditary non-polyposis colorectal cancer. *Magyar Sebeszet, 62*(2), 87-94.

ten Kate, G. L., Kleibeuker, J. H., Nagengast, F. M., Craanen, M., Cats, A., Menko, F. H., et al. (2007). Is surveillance of the small bowel indicated for lynch syndrome families? *Gut, 56*(9), 1198-1201.

Tercyak, K. P., DeMarco, T. A., Mars, B. D., & Peshkin, B. N. (2004). Women's satisfaction with genetic counseling for hereditary breast-ovarian cancer: Psychological aspects. *American Journal of Medical Genetics, 131*(1), 36-41.

Tercyak, K. P., Johnson, S. B., Roberts, S. F., & Cruz, A. C. (2001). Psychological response to prenatal genetic counseling and amniocentesis. *Patient Education and Counseling, 43*(1), 73-84.

Terreblanche, S. (2002). *A history of inequality in South Africa 1652-2002*. Pietermaritzburg: University of Natal Press.

Thibodeau, S. N., Bren, G., & Schaid, D. (1993). Microsatellite instability in cancer of the proximal colon. *Science, 260*(5109), 816-819.

Thiffault, I., Foulkes, W. D., Marcus, V. A., Farber, D., Kasprzak, L., MacNamara, E., et al. (2004). Putative common origin of two MLH1 mutations in italian-quebec hereditary non-polyposis colorectal cancer families. *Clinical Genetics, 66*(2), 137-143.

Trepanier, A., Ahrens, M., McKinnon, W., Peters, J., Stopfer, J., Grumet, S. C., et al. (2004). Genetic cancer risk assessment and counseling: Recommendations of the national society of genetic counselors. *Journal of Genetic Counseling, 13*(2), 83-114.

Tsubono, Y., Otani, T., Kobayashi, M., Yamamoto, S., Sobue, T., Tsugane, S., et al. (2005). No association between fruit or vegetable consumption and the risk of colorectal cancer in japan. *British Journal of Cancer, 92*(9), 1782-1784.

Turnpenny, P. D., Ellard, S., Emery, A. E. H., & Mueller, R. F. (2005). *Emery's elements of medical genetics.* New York: Churchill Livingstone.

Ulin, P.R., Robinson, E.T., Tolley, E.E. (2005). *Qualitative methods in public health: A field guide for applied research*. San Fransico: Jossey-Bass.

Umar, A., Boland, C. R., Terdiman, J. P., Syngal, S., de la Chapelle, A., Ruschoff, J., et al. (2004). Revised bethesda guidelines for hereditary nonpolyposis

colorectal cancer (lynch syndrome) and microsatellite instability. *Journal of the National Cancer Institute, 96*(4), 261-268.

UNESCO International Bioethics Committee. (1995). *Proceedings of the third session*. Retrieved July 2010 from unesdoc.unesco.org/images/0010/001051/105160e.pdf.

United Nations Development Programme (2004) *South African human development report 2003*. Cape Town: Oxford University Press.

van der Post, R. S., Kiemeney, L. A., Ligtenberg, M. J., Witjes, J. A., Hulsbergen-van de Kaa, C. A., Bodmer, D., et al. (2010). Risk of urothelial bladder cancer in lynch syndrome is increased, in particular among MSH2 mutation carriers. *Journal of Medical Genetics, 47*(7), 464-470.

van der Velde, N. M., Mourits, M. J., Arts, H. J., de Vries, J., Leegte, B. K., Dijkhuis, G., et al. (2009). Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? *International Journal of Cancer, 124*(4), 919-923.

van Oostrom, I., Meijers-Heijboer, H., Duivenvoorden, H. J., Brocker-Vriends, A. H., van Asperen, C. J., Sijmons, R. H., et al. (2007). Comparison of individuals opting for BRCA1/2 or HNPCC genetic susceptibility testing with regard to coping, illness perceptions, illness experiences, family system characteristics and hereditary cancer distress. *Patient Education and Counseling, 65*(1), 58-68.

Vasen, H., & Morreau, H. (2002). Familial and hereditary colorectal cancer with emphasis on the hereditary non-polyposis colorectal cancer syndrome. *Current Diagnostic Pathology, 8*(4), 241-248.

Vasen, H. F., Abdirahman, M., Brohet, R., Langers, A. M., Kleibeuker, J. H., Kouwen, M. V., et al. (2010). One to 2-year surveillance intervals reduce risk of colorectal cancer in families with lynch syndrome. *Gastroenterology,* 138(7) 2300-2306.

Vasen, H. F., & Boland, C. R. (2005). Progress in genetic testing, classification, and identification of lynch syndrome. *The Journal of the American Medical Association, 293*(16), 2028-2030.

Vasen, H. F., & de Vos tot Nederveen Cappel,W.H. (2011). Cancer: Lynch syndrome--how should colorectal cancer be managed? *Nature Reviews.Gastroenterology & Hepatology, 8*(4), 184-186.

Vasen, H. F., den Hartog Jager, F. C., Menko, F. H., & Nagengast, F. M. (1989). Screening for hereditary non-polyposis colorectal cancer: A study of 22 kindreds in the netherlands. *The American Journal of Medicine, 86*(3), 278-281.

Vasen, H. F., Mecklin, J. P., Khan, P. M., & Lynch, H. T. (1991). The international collaborative group on hereditary non-polyposis colorectal cancer (ICG-HNPCC). *Diseases of the Colon and Rectum, 34*(5), 424-425.

Vasen, H. F., Morreau, H., & Nortier, J. W. (2001a). Is breast cancer part of the tumor spectrum of hereditary nonpolyposis colorectal cancer? *American Journal of Human Genetics, 68*(6), 1533-1535.

Vasen, H. F., Moslein, G., Alonso, A., Bernstein, I., Bertario, L., Blanco, I., et al. (2007). Guidelines for the clinical management of lynch syndrome (hereditary non-polyposis cancer). *Journal of Medical Genetics, 44*(6), 353-362.

Vasen, H. F., Offerhaus, G. J., den Hartog Jager, F. C., Menko, F. H., Nagengast, F. M., Griffioen, G., et al. (1990). The tumour spectrum in hereditary non-polyposis colorectal cancer: A study of 24 kindreds in the netherlands. *International Journal of Cancer, 46*(1), 31-34.

Vasen, H. F., Stormorken, A., Menko, F. H., Nagengast, F. M., Kleibeuker, J. H., Griffioen, G., et al. (2001b). MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: A study of hereditary nonpolyposis colorectal cancer families. *Journal of Clinical Oncology, 19*(20), 4074-4080.

Vasen, H. F., Watson, P., Mecklin, J. P., & Lynch, H. T. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, lynch syndrome) proposed by the international collaborative group on HNPCC. *Gastroenterology, 116*(6), 1453-1456.

Vasen, H. F., Wijnen, J. T., Menko, F. H., Kleibeuker, J. H., Taal, B. G., Griffioen, G., et al. (1996). Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology, 110*(4), 1020-1027.

Vernon, S. W., Gritz, E. R., Peterson, S. K., Amos, C. I., Perz, C. A., Baile, W. F., et al. (1997). Correlates of psychologic distress in colorectal cancer patients undergoing genetic testing for hereditary colon cancer. *Health Psychology, 16*(1), 73-86.

Vernon, S. W., Gritz, E. R., Peterson, S. K., Perz, C. A., Marani, S., Amos, C. I., et al. (1999). Intention to learn results of genetic testing for hereditary colon cancer. *Cancer Epidemiology, Biomarkers & Prevention, 8*(4 Pt 2), 353-360.

Viiala, C. H., & Olynyk, J. K. (2008). Outcomes for women in a flexible sigmoidoscopy-based colorectal cancer screening programme. *Internal Medicine Journal, 38*(2), 90-94.

Vogelstein, B., & Kinzler, K. W. (1993). The multistep nature of cancer. *Trends in Genetics, 9*(4), 138-141.

Vorobiof, D. A., Sitas, F., & Vorobiof, G. (2001). Breast cancer incidence in south africa. *Journal of Clinical Oncology, 19*(18 Suppl), 125S-127S.

Vorster, A. (2011). Personal communication with Alvera Vorster [Division of Human Genetics, University of Cape Town].

Voskuil, D. W., Vasen, H. F., Kampman, E., & van't Veer, P. (1997). Colorectal cancer risk in HNPCC families: Development during lifetime and in successive generations. National collaborative group on HNPCC. *International Journal of Cancer, 72*(2), 205-209.

Wagner Costalas, J., Itzen, M., Malick, J., Babb, J. S., Bove, B., Godwin, A. K., et al. (2003). Communication of BRCA1 and BRCA2 results to at-risk relatives: A cancer risk assessment program's experience. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 119C*(1), 11-18.

Wagner, A., Barrows, A., Wijnen, J.T., van der Klift, H., Franken, P.F., Verkuijlen, P., et al. (2003). Molecular analysis of hereditary nonpolyposis colorectal cancer in the United States: High mutation detection rate among clinically selected families and characterization of an American founder genomic deletion of the *MSH2* gene. American Journal of Human Genetics, 72(5), 1088-1100.

Wagner, A., van Kessel, I., Kriege, M. G., Tops, C. M., Wijnen, J. T., Vasen, H. F., et al. (2005). Long term follow-up of HNPCC gene mutation carriers: Compliance with screening and satisfaction with counseling and screening procedures. *Familial Cancer, 4*(4), 295-300.

Walker, A., & Segal, I. (2002). Colorectal cancer in an african city population in transition. *European Journal of Cancer Prevention, 11*(2), 187-191.

Walker, A. R. (2001). Changes in public health in south africa from 1876. *The Journal of the Royal Society for the Promotion of Health, 121*(2), 85-93.

Walsh, M. D., Buchanan, D. D., Cummings, M. C., Pearson, S. A., Arnold, S. T., Clendenning, M., et al. (2010). Lynch syndrome-associated breast cancers: Clinicopathologic characteristics of a case series from the colon cancer family registry. *Clinical Cancer Research, 16*(7), 2214-2224.

Wang, J., Luo, M. H., Zhang, Z. X., Zhang, P. D., Jiang, X. L., Ma, D. W., et al. (2007). Clinical and molecular analysis of hereditary non-polyposis colorectal cancer in chinese colorectal cancer patients. *World Journal of Gastroenterology, 13*(10), 1612-1617.

Ward, R. L., Turner, J., Williams, R., Pekarsky, B., Packham, D., Velickovic, M., et al. (2005). Routine testing for mismatch repair deficiency in sporadic colorectal cancer is justified. *The Journal of Pathology, 207*(4), 377-384.

Warthin, A. (1913). Hereditary with reference to carcinoma. *Archives of Internal Medicine, 12*, 546-555.

Watson, R. (2008). *Nursing research: Designs and methods.* New York: Churchill Livingstone.

Watson, W. (2007). *Brick by brick: An informal guide to the history of South Africa. South Africa:* New Africa Books.

Watson, P., Lin, K. M., Rodriguez-Bigas, M. A., Smyrk, T., Lemon, S., Shashidharan, M., et al. (1998). Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. *Cancer, 83*(2), 259-266.

Watson, P., & Lynch, H. T. (2001). Cancer risk in mismatch repair gene mutation carriers. *Familial Cancer, 1*(1), 57-60.

Watson, P., Vasen, H. F., Mecklin, J. P., Bernstein, I., Aarnio, M., Jarvinen, H. J., et al. (2008). The risk of extra-colonic, extra-endometrial cancer in the lynch syndrome. *International Journal of Cancer, 123*(2), 444-449.

Watson, P., Vasen, H. F., Mecklin, J. P., Jarvinen, H., & Lynch, H. T. (1994). The risk of endometrial cancer in hereditary nonpolyposis colorectal cancer. *The American Journal of Medicine, 96*(6), 516-520.

Weil, J. (2000) *Psychosocial genetic counselling*. New York: Oxford University Press.

Weitzman, E. R., Zapka, J., Estabrook, B., & Goins, K. V. (2001). Risk and reluctance: Understanding impediments to colorectal cancer screening. *Preventive Medicine, 32*(6), 502-513.

Westenend, P. J., Schutte, R., Hoogmans, M. M., Wagner, A., & Dinjens, W. N. (2005). Breast cancer in an MSH2 gene mutation carrier. *Human Pathology, 36*(12), 1322-1326.

Westwood, G., Pickering, R. M., Latter, S., Lucassen, A., Little, P., & Karen Temple, I. (2006). Feasibility and acceptability of providing nurse counsellor genetics clinics in primary care. *Journal of Advanced Nursing, 53*(5), 591-604.

White, L. K., & Riedmann, A. (1992). Ties among adult siblings. *Social Forces, 71*, 85.

Willett, W. C., Stampfer, M. J., Colditz, G. A., Rosner, B. A., & Speizer, F. E. (1990). Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *The New England Journal of Medicine, 323*(24), 1664-1672.

Williams, D. R., Gonzalez, H. M., Williams, S., Mohammed, S. A., Moomal, H., & Stein, D. J. (2008a). Perceived discrimination, race and health in south africa. *Social Science & Medicine, 67*(3), 441-452.

Williams, D. R., Herman, A., Stein, D. J., Heeringa, S. G., Jackson, P. B., Moomal, H., et al. (2008b). Twelve-month mental disorders in south africa: Prevalence, service use and demographic correlates in the population-based south african stress and health study. *Psychological Medicine, 38*(2), 211-220.

Wilson, B. J., Forrest, K., van Teijlingen, E. R., McKee, L., Haites, N., Matthews, E., et al. (2004). Family communication about genetic risk: The little that is known. *Community Genetics, 7*(1), 15-24.

Wilson, B. J., Forrest, K., van Teijlingen, E. R., McKee, L., Haites, N., Matthews, E., et al. (2004). Family communication about genetic risk: The little that is known. *Community Genetics, 7*(1), 15-24.

Worden,N. (2007). *The making of Modern South Africa: Conquest, apartheid, democracy*, 4th edn. Oxford: Blackwell publishing.

World Health Organisation (WHO). (2006): South African Statistics. Retrieved April 2010 from http://www.who.int/countries/zaf/en/.

Wu, L. R., Parkerson, G. R.,Jr, & Doraiswamy, P. M. (2002). Health perception, pain, and disability as correlates of anxiety and depression symptoms in primary care patients. *The Journal of the American Board of Family Practice, 15*(3), 183-190.

Young, I.D. (2001). *Medical Genetics*. New York: Oxford University Press.

Zeegers, M. P., van Poppel, F., Vlietinck, R., Spruijt, L., & Ostrer, H. (2004). Founder mutations among the dutch. *European Journal of Human Genetics, 12*(7), 591-600.

DIVISION OF HUMAN GENETICS

Faculty of Health Sciences · University of Cape Town

GENETIC TESTING

Genetic testing is an examination of the DNA (basic material of hereditary) of an individual. Results of these tests may disprove or confirm a suspected fault or change (mutation) in the DNA. Genetic testing of DNA is performed on a blood sample collected from an individual.

Predictive genetic testing is a means of knowing one‘s genetic status with regard to a particular condition. To undergo a predictive genetic test implies that one is forewarned about one‘s risk of developing a particular disorder before the signs and symptoms of that condition manifest itself in an individual.

Lynch syndrome (LS) is a dominant inherited disorder with the result that all family members of an affected individual (first degree relative) are at 50% risk of developing cancer at an early age. Predictive genetic test for LS is a relatively recent option available to individuals at risk for having inherited the gene for LS. This test allows an individual a chance of knowing whether he / she has the mutation. Knowledge of one‘s genetic status, with regard to LS, allows the individual to make informed decisions about commencing preventative screening for cancer.

To take the test is a very serious decision. Therefore, it is important that subjects are well informed and understand the programme and procedures of predictive genetic testing that are necessary before finally getting the result. If after careful consideration, you decide to take the test, you will be requested to come to the Division of Human Genetics on at least 2 occasions to see the geneticist involved in running the programme. Arrangements can be made to link you with the clinical team for screening if needed.

PROGRAMME FOR PREDICTIVE TESTING – LYNCH SYNDROME

1. Telephonic contact with family members re interest in predictive genetic testing. Setting up date(s) for meeting with geneticist or genetic counsellor.
2. **1st Meeting with geneticists or counsellor:** (Group session) Information and implication of predictive genetic testing.

The outcome of this meeting can be:

- You need time to assimilate what you have heard. The registered nurses will make contact with you within a week to discuss your decision.
- You have opted to know your genetic status on LS - 1st Blood samples collected, with informed consent.

3. **2nd Meeting with geneticist or counsellor:**
   - Those who have opted to know their genetic status during the 1st meeting: meet individually with the geneticist and receive their genetic information. They have the opportunity of asking further questions pertinent to their specific situation. A second blood sample will be collected for confirmatory analysis. Contact numbers of the support team will be given. Plan of action with regard to preventative screening will be discussed. Appointments (support team + screening) can be arranged.
   - Those who have decided to know their genetic status subsequent to the 1st meeting: meet individually with geneticist to clear up any uncertainties. Meet with registered nurse to take 1st blood specimen.
4. **3rd Meeting with geneticist or counsellor:**
   - Those who have opted to know their genetic status during the 2nd meeting: meet individually with the geneticist and receive their genetic information. They have the opportunity of asking further questions pertinent to their specific situation. A second blood sample will be collected for confirmatory analysis. Contact numbers of the support team will be given. Plan of action with regard to preventative

screening will be discussed. Appointments (support team + screening) can be arranged.

GENERAL INFORMATION ON THE LS PREDICTIVE GENETIC TESTING PROGRAMME

1. We strongly recommend that you inform your family doctor of your decision to undertake the test. If you do not have a family doctor we recommend you find one. As part of the policy of this programme, we believe that the on-going medical care and support your doctor is able to give is very important to you and your family. A letter will be sent to your doctor (with your permission) to inform him/her about the programme after the 2 / 3rd meeting.
2. Support is essential and we therefore strongly advise that you choose a family member or a trusted friend to accompany you to all the meetings. (optional)
3. The final results will be given to you approximately 1 month after your blood samples have been taken and will be strictly confidential. No results will be given to you by telephone. With your permission your family doctor will be contacted and written to regarding the results.
4. If at any stage in the programme you decide you do not wish to continue, the decision is entirely yours. Your decision will in no way prejudice our relationship with you or your family. We will be happy to continue to offer you the support and help you need, within our capabilities.
5. Reactions to predictive genetic testing might vary widely. Some people who might have the predisposing genetic defect may suffer a sense of shock and grief however well they may have been prepared beforehand. People whose test is negative may feel relief but at the same time suffer guilt and anxiety. A health care professional will be available to discuss any questions / problems you might encounter after entering into the LS predictive genetic testing programme.
6. No children under the age of 18 years will be included in the LS predictive genetic test programme.
7. Those individuals who carry the mutation for LS will be counselled with regard to best practice regarding regular colonoscopic and other relevant screenings for cancer – in private or provincial settings.

8. Cost for the research leading to the finding of the genetic defect predisposing to colorectal cancer has been borne by the Division of Human Genetics. The (confirmation of diagnosis/predictive) laboratory test is available to members in families where the pre-genetic defect has been detected.

INFORMATION SHEET FOR TELEPHONIC CONTACT

PhD Genetic Counselling Research Project

AN INVESTIGATION INTO PSYCHOSOCIAL FACTORS WHICH HAVE AN IMPACT ON ACCESS TO AND UTILISATION OF THE ENDOSCOPIC SURVEILLANCE SERVICE OFFERED TO HIGH-RISK MEMBERS OF KNOWN LYNCH FAMILIES

Basic outline of information to be discussed by the Colorectal Cancer Genetic Co-ordinator when contacting individuals with LS, eligible for participation in the research study.

Background information on the study:

You have been invited to participate in a genetic counselling study conducted by a researcher of the University of Cape Town in the Division of Human Genetics.

Purpose of the study:

To gain insight into your experience of the GESC in order to evaluate the PT and surveillance programme. This will help the researcher determine the value and effectiveness of the service in an attempt to ensure the service quality is maintained or improved.

What is required to participate in the study:

Participation in a one-on-one interview with the researcher and you will be encouraged to answer all the questions in as much detail as possible. Your answers will be marked down as well as tape-recorded. All the information will remain confidential.

If you say yes:

You will be contacted by the researcher who will discuss further details of the study with you. A private venue and time will be arranged for the interview and this will occur at your convenience. There are no foreseeable risks for you as the participant,

but should you experience any form of psychological distress, please inform the researcher immediately and referral to genetic counselling services will be arranged.

If you say no:

You have every right to say no to participation in this study. Withdrawal can also take place at any time without jeopardising any medical services available to you or your family at the clinic or hospital.

PHD GENETIC COUNSELLING RESEARCH PROJECT

AN INVESTIGATION INTO PSYCHOSOCIAL FACTORS WHICH HAVE AN IMPACT ON ACCESS TO AND UTILIZATION OF THE ENDOSCOPIC SURVEILLANCE SERVICE OFFERED TO HIGH-RISK MEMBERS OF KNOWN LYNCH FAMILIES

INFORMATION AND CONSENT FORM

STATEMENT BY PARTICIPANT

I, ……. Living at (address)

…….

confirm that:

1. I have been invited to participate in the above research project, which has been initiated through the Division of Human Genetics, University of Cape Town because I am currently involved in the surveillance and/or predictive testing programme.

2.1 I understand that the aim of this study is to:

- To appraise the GESC from the users' perspective using face-to-face interviews to ascertain their experiences and satisfaction with the clinic;
- To measure the level of the adherence to recommended surveillance screening guidelines;
- To determine the impact of socio-economic status, education, physical barriers and psychosocial factors on adherence to the recommended surveillance programme;
- To determine the uptake of PT among participants and their family members;
- To identify and explore the referral pathways and communication networks leading to the GESC

2.2 I understand that the interview will take place in my home or at another venue of my choice and that it may take one or two visits of up to two hours each.

2.3 I am aware that this is a once off procedure that will be implemented in 2009/2010 at a time convenient to me.

2.4 I understand that some of the questions may make me angry or sad, but the risks to me from the study are minimal. The researcher will refer me to a genetic counsellor if necessary. She will show me respect, acceptance and empathy during the interview.

3.1 I have been assured that all the information will be handled confidentially. Information may be used for a thesis, publications in scientific journals and at presentations at professional congresses, but names will not be included.

3.2 I understand that the interview will be tape recorded so that the researcher does not have to write too much during the interview. The tape will be stored in a safe place until the research has been written up and will then be destroyed immediately. The data stored on the computer will have a numerical code only and my name does not appear anywhere.

4.1 I have been assured that the recorded and transcribed information discussed at the meeting will only be made available to the researcher‘s supervisors with my study code number and that they do not know that it refers to my name.

5. I have not been persuaded to consent to taking part in the study and I have been informed that I my refuse to participate in this project, that I may stop participating at any stage, and that such refusal or stoppage will not in any way negatively affect my future access to medical and genetic services to which I am entitled.

6. ……. has explained the information of the study to me in English/Afrikaans. I am proficient in that language and my questions have been answered satisfactorily.

7. I understand that there will be no medical benefits to me from this study.

8. I have been assured that participation in this project will not lead to additional costs for me and I will not benefit from it financially.

I hereby declare that I voluntarily agree to participate in the above research study

Signed at:
(address) ……. on ……/…..…/…….

…… ……..
Participant‘s signature Witness

I hereby declare that I agree to have my interview audiotape recorded

Signed at:
(address) ……. on ……/…..…/…..

…… ……..
Participant‘s signature Witness

I give permission/consent for any requested photographs to be taken

Signed at:
(address) ……. on ……/…..…/…..

…… ……..
Participant's signature Witness

IMPORTANT INFORMATION

Dear participant,

Thank-you very much for your participation in this study. If you have any questions about the research concerning:

1. problems due to the research, or
2. questions relating to the information about the project

you can contact me or Prof. Raj Ramesar on:

Zandre Bruwer (021) 406 6373
E-mail: zbruwer@uct.ac.za

Prof Raj Ramesar (021) 406 6337

If you have any questions relating to your right as a participant, contact Prof. Marc Blockman, the chairman of the ethics committee of the University of Cape Town on (021) 406 6492

GENETIC ENDOSCOPIC SURVEILLANCE CLINIC (GESC) RESEARCH PROJECT

GROUP A: INTERVIEW SCHEDULE - English version

SECTION A - DEMOGRAPHIC DATA AND PERSONAL HISTORY

1. Gender	Male[1]	Female[2]			A1
2. Age					A2
3. Ethnic group	Mixed Ancestry[1]	White[2]			A3
4(a). Occupation	Employed[1]	Unemployed[2]	Part-time/casual[3]		A4a
4(b). Type of work/occupation?					A4b
Managerial, professional, semi-professional[1]					
Clerical, sales, service[2]					
Skilled agricultural, craft, operators[3]					
Elementary occupations[4]					
Other[5]					
4(c). If currently unemployed, were you previously employed?					A4c
Yes[1]		No[2]			
4(d). Reason for unemployment:					A4d
5(a). Monthly household income:					A5a
No income[1]	Grant [2]		R1 - R400[3]		
R401 - R800[4]	R801 - R1600[5]		R1601 - R3200[6]		
R3201- R6400[7]	R6401 - R12 800[8]		R12 801 - R25 600[9]		
R25 601 - R51 200[10]	R51 201 - R102 400[11]		R102 401 - R204 800[12]		
R 204 801 and more[13]					
5(b). How many people are dependant on this income?					A5b
5(c). Type:					A5c
All pay/disability grant[1]					
Child support grant/care dependancy grant[2]					
Pension[3]					
5(d). Number of grants per household:					A5d
5(e). Total income of grants:					A5e
R1 - R400[1]	R401 - R800[2]	R801 - R1600[3]	R1601 - R3200[4]		
R3201- R6400[5]	R6401 - R12 800[6]				
6. Education	**Years completed at:**				
	(a) Junior school		(out of 7)		A6a
	(b) Senior school		(out of 5)		A6b
	(c) College/University		Yes[1]	No[2]	A6c
7. Was there any reason for not completing school or college?					A7
8. Marital status	Single[1]	Widow[2]	Married/Partner[3]	Divorced[4]	A8
9. Home language	English[1]		Afrikaans[2]		A9

The following information will be obtained by drawing your family pedigree. This drawing will also be used to answer the questions in Section G.

10. Number of children (all biological children):	A10

Name of child	M/F	Age of child	Additional notes

11(a). How many children eligible for predictive testing?	A11a
11(b). How many children eligible for predictive testing have been tested?	A11b
12(a). Number of siblings eligible for testing when it became available to your family?	A12a
12(b). Number who have been tested?	A12b

Name of sibling	M/F	Age of brother/sister	Additional notes

13(a). Affected parent:	Male[1]	Female[2]	Unaffected male[3]	Unaffected female[4]	A13a
	Does not know[5]				
13(b).	Tested before[1] or after proband[2]:		Never tested[3]		A13b
14(a). If the parent was affected, are they still currently alive?			Yes[1]	No[2]	A14a
14(b). If your parent was affected, what type of cancer did they have?					A14b
CRC(colorectal cancer)[1]	Endometrial[2]	Breast[3]	Other[4]	No cancer[5]	
15. Your age (the earliest memory), when you found out/knew your parent had cancer?					A15
16(a). Family size (nuclear)					A16a
16(b). Family size (total)					A16b
17. Have you had to care for anyone with cancer in your family?			Yes[1]	No[2]	A17
18. In terms of your family history of cancer how do you feel about your risk of developing cancer?					A18
19. Referral to clinic:					A19
20. What were you told, or what did you expect?					A20
21 (a). Year first seen at the mobile endoscopic clinic (MEC)/ hospital clinic				Year:	A21a
21 (b). Seen at the:	MEC[1]			Hospital clinic[2]	A21b
22. Seen for:	Colonoscopy[1]	Genetic testing[2]	Both[3]		A22
23. Affected with colorectal cancer (CRC) at this stage		Yes[1]	No[2]	Symptomatic[3]	A23
24. Previously affected with CRC		Yes[1]	No[2]	Polyps[3]	A24
25. Age when diagnosed with CRC/polyp?					A25

26. Affected with any other cancer?	Yes[1]	No[2]	A26
27. Age affected with this cancer?			A27
28. Test result (mutation identified)	MLH1[1]	MSH2[2]	A28
29. Residential area: Western Cape[1]	Northern Cape[2]		A29
30. Location: Rural[1]	Urban[2]		A30
31. Total number of family members affected with cancer in the nucleur family (parent,sibling,child)			A31

SECTION B - KNOWLEDGE OF LYNCH SYNDROME

1. The following section is not to be viewed as a test. The questions relate to what you understand about Lynch Syndrome (LS) and how the condition has been explained to you at the clinic.

Please answer yes or no to the following questions (adapted from Domanska et al 2009).

(a) CRC affects ~ 4-5% of all individuals in South Africa	Yes[1]	No[2]	B1a
(b) Individuals who carry the gene for LS will definitely develop cancer	Yes[1]	No[2]	B1b
(c) Indivduals who do not carry the gene will never develop CRC	Yes[1]	No[2]	B1c
(d) Females with LS have an additional risk of endometrial cancer	Yes[1]	No[2]	B1d
(e) Females with LS have an additional risk of ovarian cancer	Yes[1]	No[2]	B1e
(f) Colonoscopy is only useful in indivduals with LS when there are bowel symptoms	Yes[1]	No[2]	B1f
(g) Indivduals with LS need regular colonocopies	Yes[1]	No[2]	B1g
(h) Indivduals with LS will pass the faulty gene on to 25% of their children	Yes[1]	No[2]	B1h
(i) Tumour tissue can be used to diagnose LS	Yes[1]	No[2]	B1i
(j) Blood samples can be used for genetic testing	Yes[1]	No[2]	B1j
(k) The disease is most often inherited from the male side of the family	Yes[1]	No[2]	B1k

2. What is the most important thing about LS that you are aware of?				B2
(Cause, signs and symptoms, age of onset, inherited cancer predisposition)				
3(a). Do you know anything else about the condition, which you choose not to tell people?				B3a
3(b). If yes, what?				B3b
4. Were your parents very secretive about the cancer in the family (kept their diagnosis a secret)?				B4
5. What symptoms would make you worry that you might have LS?				B5
6. What do you know about the symptoms in your family?				B6
7. What risk do you have of developing LS?				B7
8. Does it affect males and females equally?				B8
9. What chance do the following individuals have of developing LS?				
(a) Brothers and sisters				B9a
(b) Children				B9b
(C) Heard of the 50% risk?	Yes[1]	No[2]		B9c
10. Where did you learn about LS/how did you come to learn about your risk for CRC?				B10
11(a). Did you seek further information	Yes[1]	No[2]		B11a
11(b). Did you have any resources available to use:				B11b
12(a). If Yes, what terminology did you use/what name do you refer to it as?				B12a
Cancer [1]	CRC [2]	HNPCC/LS [3]	Other[4]	

12(b). Have you heard of the term HNPCC/LS?	Yes[1]	No[2]	B12b
13(a). Have you received any handouts or information on LS?	Yes[1]	No[2]	B13a
If yes: **(b) Do you still have it?**	Yes[1]	No[2]	B13b
(c) Did you find it useful?	Yes[1]	No[2]	B13c
14. When was the first time that the genetics of LS was discussed with you?			B14
First session[1]	At a later stage[2]	Can't remember[3] Never[4]	
15. How often is the genetics/inheritance of LS discussed with you?			B15
16. Was the inherited risk to the children discussed with you?			B16
17. How did you feel when you heard this information?			B17
18.Would this information have impacted on your decision to have a family (children)?			B18
19. How has your parent's or (family member's) cancer affected the way you deal with your risk, in terms of:			
(a) Surveillance (similar, different because of how they dealt with it)			B19a
More adherent[1]			
The same/no effect[2]			
Less adherent[3]			
Did not know parent/family member with cancer[4]			
Other[5]			
(b) Watching for symptoms (go to Dr immediately, denial, worry at first sign of something wrong)			B19b
Yes[1]	No[2]		

SECTION C – ENDOSCOPIC SURVEILLANCE SERVICE

1. What transport was used to get to the clinic?				
(a). Type				C1a
Walked[1]	Own transport[2]	Borrowed a car[3]	Public transport (bus/taxi)[4]	
Free hospital ambulance[5]		Other[6]		
(b). Free/cost		Free[1]	Cost[2]	C1b
(c). Arranged by:		You[1]	Someone else[2]	C1c
2. How long does it take you to get to the MEC/ hospital clinic?				C2
3. Have you received a colonoscopy?		Yes[1]	No[2]	C3
4. How many/how often do you go (every year, missed some etc) (Self-report)				C4
4(c). How often do you think you should go for a colonoscopy/sigmoidoscopy?				C4c
4(d). If you have had an operation for cancer, do you know that you must come for yearly sigmoidoscopy's?				C4d
		Yes[1]	No[2]	
5. As a woman, do you go for gynaecological surveillance? (what was done)		Yes[1]	No[2]	C5
6. How often?				C6
7. How has your experience been of a colonoscopy?				
(a). Colo-prep (taste, amount of fluid, nauseous)				C7a
(b). Toilet facilities (at home, clinic, did you manage without facilities)				C7b
(c). Procedure (medication, discomfort of scope, stress associated with procedure/outcome)				C7c

(d). If you have never been what have you heard about it?	C7d
8. Would you go for a colonoscopy again? Yes[1] Maybe[2] No[3]	C8

9. The following questions relate to why you go/ do not go for colonoscopic surveillance:			
	Main reason - 1	Play's a part in going - 2	Not a reason -3
What are your reasons for going for a colonoscopy?			
(a) Maintain health			C9a
(b) Recent death/affected relative in family			C9b
(c) Family member/doctor's recommendation			C9c
(d) Polyp/cancer found previously			C9d
(e) Is there any other reason why you go for colonoscopies?			C9e

Those times that you did not go	
10. What are your reasons for not going for a colonoscopy?	
(a) Colon preparation	C10a
(b) Discomfort of procedure	C10b
(c) Reported painful experience	C10c
(d) Transport problems	C10d
(e) Do not think that I need it	C10e
(f) Is there any other reason why you do not go for colonoscopies?	C10f

11. Were the results of you colonoscopy discussed with you?	Yes[1]	No[2]	C11
12(a). Can you explain your results to me (what it means in terms of your health and management. What did they say to you after your last colonoscopy)	Knows[1]	Does not know[2]	C12a
12(b). What is the purpose of the colonscopy?	Knows[1]	Does not know[2]	C12b
12(c). What does it mean if they identify a polyp during the colonoscopy?	Knows[1]	Does not know[2]	C12c
Does not know what a polyp is[3]			
12(d). Why do you think the procedure must be done every year?	Knows[1]	Does not know[2]	C12d
13(a). Did you know when to come again?			C13a
13(b). If no, why not:			C13b
14. Do you have the number of a contact person at the clinic?	Yes[1]	No[2]	C14
15. If you missed an appointment, did you reschedule?	Yes[1]	No[2]	C15
16. Would it be possible to get a colonoscopy elsewhere?	Yes[1]	No[2]	C16

SECTION D - SATISFACTION WITH GESC

1. This section relates to the satisfaction with your previous clinic appointments. Please answer this as truthfully as possible, everything will remain confidential from the staff at the clinic. It is only through your honesty that the service could be improved.

This section requires you to answer yes or no to the following statements:			
(a) Everyday language was used to explain LS (home language was used, easy to understand concepts used to explain)	Yes[1]	No[2]	D1a
(b) Everything I wanted to know about LS was explained at the clinic[1,2] (cause, age of onset, symptoms, reason for surveillance)	Yes[1]	No[2]	D1b
(c) The counselling received helped me cope better with my condition/ risk of developing the condition[4]	Yes[1]	No[2]	D1c
(d) I will follow the clinics advice because I think they are absolutely right[2] (Come for a colonoscopy every year/gynae visits etc/talk to family about risk)	Yes[1]	No[2]	D1d
(e) I understand why my family has a higher risk than other families of developing cancer	Yes[1]	No[2]	D1e
(f) The time I spent at the GESC was long enough to deal with everything I wanted to discuss[2] (how much time did you spend with the staff, did you feel this was long enough)	Yes[1]	No[2]	D1f
(g) The Dr/nurse/counsellor was easy to reach after the clinic consultation for any questions/concerns that I had[3] (Were they contacted, was there a need to contact)	Yes[1]	No[2]	D1g
(h) Were any of your questions unanswered?[1] (did you have any unanswered questions at visit, after visit, were they answered)	Yes[1]	No[2]	D1h

[1]Westwood 2006.
[2]Poulton 1996.
[3]Groenewegen et al 2005.
[4]Shiloh et al 1990.

SECTION E - COMMUNICATION IN THE FAMILY

1. Can you tell me about the time (how you felt) when you received your positive test result? (the time leading up to the result, your expectations of the result, your reaction, how you are coping)	E1
2. Did you seek any emotional support?	E2
3. Did anyone know that you were going to receive your result that day?	
Yes[1] No[2]	E3
4(a). Did you tell anyone about your result that day?	E4a
(b) Who:	E4b
(c) Why them:	E4c

5. Using the pedigree, indicate who on the list has been told and use the table below to select the most appropriate answer as to why they were told.	E5

List of relatives	Told[1]	Not told[2]	Too young[3]	Passed away[4]	
(a) Partner					E5a
(b) Parent with CRC/increased risk					E5b
(c) Parent without increased risk					E5c
(d) Children - list A10:					E5d
(e) Siblings - list A12:					E5e
(f) Friends					E5f
(g) Other					E5g
6. Were these people told due to a different reason than that of the first person you told?					E6

7(a). LS is an inherited form of cancer and the rest of your family would also be at-risk for the condition. Have you informed any family member (sibs, parents, aunts, uncles, cousins) about testing and/or screening?

Yes[1] No[2]	E7a
(b). If no: why not?	E7b
(c). Was this person(s) unaware of the programme or non-adherent?	E7c
New[1] Non-adherent[2] Has not come for genetic testing[3]	
(d). How long after you received your result, did you tell them?	E7d
(e). Did you mention your test result when discussing this risk with them? Yes[1] No[2]	E7e
8(a). Have your children been informed that they may be at risk of developing LS?	E8a
Yes[1] No[2]	
8(b). Age information discussed with them?	E8b
8(c). If you have informed them already, why did you choose this specific time?	E8c
8(d). Did you tell them about the genetic test (blood test)? Yes[1] No[2]	E8d
8(e). Did you tell them about surveillance? Yes[1] No[2]	E8e
9. Predictive testing is usually offered from 18 years. At what age do you think people should be tested?	
18 years is the right time[1] Should be earlier[2] Should be later[3]	E9
10. How often do you discuss LS with your family members?	E10
11(a). Is there anything that would have helped you tell your family that they are at-risk?	E11a
11(b). Is there anything you want more information on?	E11b
12. Who usually communicates important information to the rest of the family?	E12
13. Who should tell the family about the familial risk? Family[1] Clinic[2]	**E13**

SECTION F - GENERAL HEALTH OF PARTICIPANT

1(a). Since your last visit to the clinic have you had any bowel-related concerns? Yes[1] No[2]	F1a
1(b). If yes, what have you done about this?	F1b
2. Has testing positive for the gene predisposing to the cancer in your family influenced your eating habits?	F2
Yes[1] No[2]	
3. Has testing positive for the gene predisposing to the cancer in your family influenced your drinking habits?	F3
Yes(less)[1] No[2] Not applicable[3]	
Yes(more)[4]	
4. Has testing positive for the gene predisposing to the cancer in our family, influenced your smoking habits?	F4
Yes(less)[1] No[2] Not applicable[3]	
Yes(more)[4]	
5. Screening behaviour (information from database):	
(a). Attendance rate for colonoscopy (adherence group)	F5a
(b). Attendance and type of gynaecological examinations (Women only) Yes[1] No[2] Once only[3]	F5b
(c). Type of genetic test PT[1] Diagnostic test[2]	F5c
(d). Development of polyp or cancer? Polyp[1] Cancer[2] Not applicable[3]	F5d
(e). Site of cancer	F5e

(f). History of surgery	Yes[1]	No[2]	Type	F5f
(g). Chemotherapy and or radiation	Yes[1]	No[2]		F5g

DUKE-AD SCALE – Pakerson and Broadhead (1997)			
6. The following questions are about your health and feelings experienced.			
Please read each question carefully and select the best answer. Do not spend too much time on any statement. Ther are no wrong or right answers.			
	Yes, describes me exactly	Somewhat describes me	No, doesn't describe me at all
(a) I give up too easily	2	1	0
(b) I have difficulty concentrating	2	1	0
(c) I am comfortable being around people	0	1	2
DURING THE PAST WEEK: **How much trouble have you had with:**	**None**	**Some**	**A lot**
(d) Sleeping	0	1	2
(e) Getting tired easily	0	1	2
(f) Feeling depressed or sad	0	1	2
(g) Nervousness	0	1	2
Total Score			F6

CANCER WORRY SCALE- (Lerman et al 1991).

7. Please answer the following questions with the statement which best describes how you felt: In the past month...

	Not at all or rarely - 1	Sometimes - 2	Often - 3	Almost all the time -4
(a) How often have you thought about your own chances of developing cancer?	___1	____2	___3	____4
(b) How often have you worried about your own chances of developing cancer?	___1	____2	___3	____4
(c) How often has thoughts about getting cancer affected your mood?	____1	___2	___3	____4
(d) How often have thoughts about getting cancer affected your ability to perform daily activities?	____1	____2	___3	_____4

Total score	F7

SECTION G - RESEARCH			
1. Have you been involved in the CAPP study?	Yes[1]	No[2]	G1
2. What was your experience of the study like?			G2
3(a). Have you been involved in any other research studies?	Yes[1]	No[2]	G3a
3(b). What has this been like?			G3b
3(c). Would you like to be involved in future research studies?			G3c

GENETIC AND ENDOSCOPIC SURVEILLANCE CLINIC (GESC) RESEARCH PROJECT

GROUP B: INTERVIEW SCHEDULE - English version

SECTION A - DEMOGRAPHIC DATA AND PERSONAL HISTORY

1. Gender	Male[1]	Female[2]			A1
2. Age					A2
3. Ethnic group	Mixed Ancestry[1]	White[2]			A3
4(a). Occupation **Presently:**	Employed[1]	Unemployed[2]	Part-time/casual[3]		A4a
4(b). Type of work if employed:					A4b
Managerial, professional, semi-professional[1]					
Clerical, sales, service[2]					
Skilled agricultural, craft, operators[3]					
Elementary occupations[4]					
4(c). If currently unemployed were you previously:	Employed[1]	Unemployed[2]			A4c
4(d). Reason for unemployment:					A4d
5(a). Monthly household income:					A5a
No income[1]	Disability grant [2]	R1 - R400[3]			
R401 - R800[4]	R801 - R1600[5]	R1601 - R3200[6]			
R3201- R6400[7]	R6401 - R12 800[8]	R12 801 - R25 600[9]			
R25 601 - R51 200[10]	R51 201 - R102 400[11]	R102 401 - R204 800[12]			
R 204 801 and more[13]					
5(b). How many people (including you) are dependant on this income?					A5b
5(c). Type:					A5c
Disability grant(All pay)[1]					
Child support grant/care dependancy grant[2]					
Pension[3]					
5(d). Number of grants per household:					A5d
5(e). Total income of grants:					A5e
R1 - R400[1]	R401 - R800[2]	R801 - R1600[3]	R1601 - R3200[4]		
R3201- R6400[5]	R6401 - R12 800[6]				
6. Education	**Years completed at:**				
	(a) Junior school	(out of 7)			A6a
	(b) Senior school	(out of 5)			A6b
	(c) College/University	Yes[1]	No[2]	N/a[3]	A6c
7. Was there any reason for not completing school or college?					A7
8. Marital status:	Single[1]	Widow[2]	Married/Partner[3]	Divorced[4]	A8
9. Home language:	English[1]	Afrikaans[2]	Both[3]	Other[4]	A9
10(a). Number of children (all biological children):					A10a
10(b). Number of children eligible for testing:					A10b
10(c). Number of eligible children who have been tested?					A10c
11(a). Affected parent:	Male[1]	Female[2]	Unaffected male[3]	Unaffected female[4]	A11a

11(b). Tested:	Before[1] or after proband[2]		Never tested[3]	A11b
12. Are they still alive?		Yes[1]	No[2]	A12
13(a). Your age when your parent was affected?				A13a
13(b). Exposure to CRC				
None[1]	Affected relatives elsewhere[2]	Lived with affected family member with CRC[3]		A13b
Lived with affected family member who died of CRC[4]	Other[5]			
14(a). Number of siblings (lineage of affected or mutation positive parent).				A14a
14(b). Number of eligible siblings:				A14b
14(c). Number of eligible siblings who have been tested?				A14c
15(a). How would you feel if you tested positive? (very anxious, not too worried, etc)				A15b

SECTION D1 - GENETIC COUNSELLING PERSPECTIVES AND SATISFACTION

1. The following list describes the information that may have been covered during your session with the Dr/Sr/counsellor when blood was taken for genetic testing.

How important was each of the following to you?

	Very important - 1	Important - 2	Not important - 3
(a) Cause of the condition			
(b) Explanation on why the condition is passed on from one generation to the next			
(c) The medical name for the condition			
(d) Explanation on who else is at-risk (in the family) for LS			
(e) If treatments are available for LS			
(f) Potential treatments that may become available in the future			
(g) Information on what will happen to someone with the condition as time goes by			
(h) Availability of a genetic test to see if I will get this condition			
(i) To be able to contact other families affected with the condition for support			
(j)The information covered in the session should be written down for future reference			
(k) Is there a test for this condition in pregnancy			

2(a). If one could test for LS during pregnancy, what would your thoughts be on TOP if the foetus tested positive for the condition?				
Agree[1]	Disagree[2]	Disagree but okay for others to do it[3]	Other[4]	D2a
2(b). If disagree (2) why:				D2b
Morals/Religion1		Not a poor enough prognosis-something can be done[2]		
Other[3]				

3. Satisfaction with Genetic Counselling (De Marco et al 2004).
Please rate each statement:
Please answer this section as truthfully as possible, everything will remain confidential from the staff at the clinic. It is only through your honesty that the service can be improved.

	Strongly disagree - 1	Somewhat - 2	Agree strongly - 3	
(a). The staff member of the clinic seemed to understand the stress I was facing				D3a
(b). They helped me to identify what I needed to know to make decisions about the blood test and surveillance				D3b
(c). I felt better about my health after meeting with them				D3c
(d). The session was about the right length of time				D3d
(e). They were truly concerned about my well-being				D3e
(f). The session was valuable to me				D3f

SECTION D2 - PREDICTIVE TESTING AND COUNSELLING PROGRAMME

1. How did you hear about the clinic Clinic[1] Self[2] GP[3] Family[4] Other[5]	d1
2. How long after you heard about the clinic did you come for predictive testing?	d2
3. What made you decide to go to the clinic?	d3
4. Did any of the following statements affect your decision to be tested (predictive blood test)	

	A lot-1	moderatley-2	Not at all-3	
(a) Planning for the future				d4a
(b) Marital decisions				d4b
(c) Reproductive decisions				d4c
(d) Clarifying risk for (future) children				d4d
(e) Employment decisions				d4e
(f) Reducing uncertainty				d4f
(g) Dr recommended it				d4g
(h) Self-evident				d4h
(i) Family member/partner urged me to do it				d4i
(j) To find out if surveillance needed to be continued				d4j
(k) Other reasons, please state				d4k

5. What do you think is the purpose of predictive genetic testing? Knows[1] Does not know[2]	d5
6. Should you test positive for the gene, how would you feel about the surveillance?	d6

7. Duke anxiety and depression scale- (Parkerson and Broadhead 1997).

The following questions are about your health and feelings experienced.
Please read each question carefully and select the best answer. Do not spend too much time on any statement.
There are no right or wrong answers.

	Yes, describes me exactly	Somewhat describes me	No, doesn't describe me at all
(a) I give up too easily	2	1	0
(b) I have difficulty concentrating	2	1	0
(c) I am comfortable being around people	0	1	2
DURING THE PAST WEEK:	**None**	**Some**	**A lot**
How much trouble have you had with:			
(d) Sleeping	0	1	2
(e) Getting tired easily	0	1	2
(f) Feeling depressed or sad	0	1	2
(g) Nervousness	0	1	2
Total Score			d7

Cancer worry scale- Lerman et al 1991

8. Please answer the following questions with the statement which best describes how you felt:

In the past month...

	Not at all or rarely- 1	Sometimes - 2	Often - 3	Almost all the time- 4
(a) How often have you thought about your own chances of developing cancer?	1	2	3	4
(b) How often have you worried about your own chances of developing cancer?	1	2	3	4
(c) How often has thoughts about getting cancer affected your mood?	1	2	3	4
(d) How often have thoughts about getting cancer affected your ability to perform daily activities?	1	2	3	4

Total Score	d8

Second interview – immediately after result delivery session

1. Duke anxiety and depression scale- (Parkerson and Broadhead 1997).

The following questions are about your health and feelings experienced.

Please read each question carefully and select the best answer. Do not spend too much time on any statement. There are no right or wrong answers.

	Yes, describes me exactly	Somewhat describes me	No, doesn't describe me at all
(a) I give up too easily	2	1	0
(b) I have difficulty concentrating	2	1	0
(c) I am comfortable being around people	0	1	2
DURING THE PAST WEEK:	**None**	**Some**	**A lot**
How much trouble have you had with:			
(d) Sleeping	0	1	2
(e) Getting tired easily	0	1	2
(f) Feeling depressed or sad	0	1	2
(g) Nervousness	0	1	2
Total Score			d1

Cancer worry scale – (Lerman et al 1991).

2. Please answer the following questions with the statement which best describes how you felt:

In the past month...

	Not at all rarely- 1	Sometimes - 2	Often - 3	Almost all the time - 4
(a) How often have you thought about your own chances of developing cancer?	1	2	3	4
(b) How often have you worried about your own chances of developing cancer?	1	2	3	4
(c) How often has thoughts about getting cancer affected your mood?	1	2	3	4
(d) How often have thoughts about getting cancer affected your ability to perform daily activities?	1	2	3	4

Total Score	d2

Section H (Third interview) – one month after result delivery

1. How did you feel immediately after you received your genetic test result?	H1
2. Are you satisfied with your decision to go for predictive genetic testing?	H2
Yes[1] No[2]	
3. Do you trust the test result?	H3
Yes[1] No[2] Other[3]	
4. Now that you know your result, would you have taken the test in the first place?	H4
Yes[1] No[2]	
5(a). Would you advise other family members to be tested: Yes[1] No[2]	H5a
5(b). Yes, and why[1]?	H5b
5(c). No, and why[2]?	H5c
6. Predictive testing is usually offered from 18 years, at what age do you think people should be offered testing?	
	H6
7. Do you think blood should be taken on the same day as the pre-test counselling (first session with counsellor)?	
Yes[1] No[2]	H7
8. Were you happy with the amount of time that it took for you to receive your test results (how long did you wait, were you told how long it would take)?	
Yes[1] No[2]	H8
9. How often did you think of your test result during this waiting period?	
Not at all[1] Every now and then[2] A lot[3] Almost all the time[4]	H9
10. What would have helped you cope better during this waiting time?	H10
11(a). Have you seen someone outside of the clinic for emotional support (social worker, psychologist, Sr at local clinic, family member)?	
Yes[1] No[2]	H11a
11 (b). If yes, who?	H11b
12 (a). Have you told anyone about your PT result?	H12a
12 (b). If yes, who?	H12b

Duke anxiety and depression scale (Parkerson and Broadhead 1997).

The following questions are about your health and feelings experienced.

Please read each question carefully and select the best answer. Do not spend too much time on any statement. There are no right or wrong answers.

	Yes, describes me exactly	Somewhat describes me	No, doesn't describe me at all
(a) I give up too easily	2	1	0
(b) I have difficulty concentrating	2	1	0
(c) I am comfortable being around people	0	1	2

DURING THE PAST WEEK:	**None**	**Some**	**A lot**
How much trouble have you had with:			
(d) Sleeping	0	1	2
(e) Getting tired easily	0	1	2
(f) Feeling depressed or sad	0	1	2
(g) Nervousness	0	1	2
Total Score			H1

CANCER WORRY SCALE – (Lerman et al 19991).

2. Please answer the following questions with the statement which best describes how you felt:

In the past month...

	Not at all / rarely- 1	Sometimes - 3	Often - 4	Almost all the time - 5
(a) How often have you thought about your own chances of developing cancer?	1	2	3	4
(b) How often have you worried about your own chances of developing cancer?	1	2	3	4
(c) How often has thoughts about getting affected your mood?	1	2	3	4
(d) How often have thoughts about getting cancer affected your ability to perform daily activities?	1	2	3	4

Total Score	H2

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

06 May 2009

REC REF: 213/2009

Prof R Ramesar & Ms Z Bruwer
Human Genetics

Dear Prof Ramesar & Ms Bruwer

PROJECT TITLE: AN INVESTIGATION INTO PSYCHOSOCIAL FACTORS WHICH HAVE AN IMPACT ON ACCESS TO AND UTILIZATION OF THE MOBILE ENDOSCOPIC SURVEILLANCE SERVICE OFFERED TO HIGH-RISK MEMBERS OF KNOWN LYNCH FAMILIES.

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 10th May 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

S Thomas

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual or final approval, including any documentation described above			
☑ Approved	Annual progress report		
OR ☐ Approved	Study closure report		
☐ Not approved	See attached comments		
Expiry date	15 MAY 2012		
Signature Chairperson of the HREC		Date	19·4·11

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual or final approval, including any documentation described above.			
☐ Approved	Annual progress report		
OR ☐ ~~Approved~~	Study closure report		
☐ Not approved	See attached comments		
Expiry date			
Signature Chairperson of the HREC		Date	24/6/11

SOCIAL SECURITY GRANTS IN SOUTH AFRICA

Social security grants are financed through nationally collected tax revenues and are available in the form of:

Old Age Grant

This grant is available to males and females over the age of 60 years, where the spouse complies by the means test and the recipient is not in the possession of another social grant. R1010 is allocated per month.

Disability Grant

Males between the ages of 18 to 59 years and females between the ages of 18 to 64 years, with a disability (which declares the individual mentally or physically unfit to work) and, who are not receiving any other social grants are eligible for the R1080 per month.

Grant in Aid

This grant is available to persons with a disability grant but requiring full-time attendance for care owing to their physical or mental disabilities. R250 per month is made available for the care-giver.

Child Support Grant

R250 per month per child is made available with this social grant. Applicants are required to be the child‘s primary care giver and over the age of 16 years.

Care Dependency Grant

This grant is available to parents of children who are one to 18 years of age with a disability. R1080 is provided per month.

Foster Child Grant

This grant of R710 per month is available to a foster parent, holding a court order indicating foster parent status and complying with the means test. The grant is available until the foster child turns 18 years of age (Government Gazette Act Nos R417 of 1998; and 52 of 1992; South African Government Services: Child grants and older person grants 2010).

DIVISION OF HUMAN GENETICS

Faculty of Health Sciences · University of Cape Town

Name Surname……..

Address……

Date……..

Dear …….

RE: Genetic testing for your family

The Division of Human Genetics at the University of Cape Town has been doing genetic research on colorectal cancer since 1987, in order to improve clinical management of the disorder.

The Colorectal Cancer Registry at the University of Cape Town received blood samples from members of your family, which were donated for research. Our research has recently led to the discovery of a specific genetic change which results in members of your family, who are carrying the change, having an inherited tendency to develop cancer. Even if people who carry the genetic change have not developed cancer themselves, they can pass this inherited tendency to their children. **If a person has an increased chance of developing cancer, there are effective ways of reducing this risk.**

Please contact us for further information or if you would like to find out more about the services available to you. You can be assured that the information we give you and any information we receive from you is treated confidentially.

We urge you to take this matter seriously as this information can be life-saving.

Contact details:

Genetic counselling service – University of Cape Town, Faculty of Health Sciences:
Tel: (021) 406 6373 or (021) 406 6304

Yours sincerely

_____

Date: ……/……/……

DIVISION OF HUMAN GENETICS
AND GROOTE SCHUUR HOSPITAL

Dear …….

RE: Leave of absence

The Division of Human Genetics at the University of Cape Town together with Groote Schuur Hospital has seen ……..…… on the ……/……/…...

This patient was seen at the …….. (clinic or hospital) for a procedure on the ……/……/…… which required preparation on the ……/……/…… prior to their scheduled appointment.

Yours sincerely

_____

Date: ……/……/……