A comparative cost analysis of two screening strategies for colorectal cancer in Lynch Syndrome in a tertiary hospital, South Africa

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DECLARATION

I, Yasmina Johnson, hereby declare that the work on which this dissertation / thesis 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.

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Dedication

To Fazel, I could not have done this without you.

To my family, all of you, THANK YOU.

Abstract

Individuals with Lynch Syndrome (LS) have a 25% to 75% lifetime risk of colorectal cancer and the cancer generally presents at an early age. Establishing the costs of strategies to prevent or delay the onset of cancer is, thus, desirable. This study compared the cost of two screening approaches - colonoscopy only (Strategy 1) versus genetic testing for LS followed by colonoscopy for the individuals that tested positive for LS (Strategy 2).

A comparative cost analysis was conducted at a tertiary hospital, from the health provider perspective, using a micro-costing, ingredient approach. Probands that were selected, according to the Revised Bethesda Criteria, for genetic testing between 01 November 2014 and 30 October 2015, and their first degree relatives (high risk relatives) were evaluated according to Strategy 1 and Strategy 2. Total costs per strategy were estimated and compared. Sensitivity analyses were performed on adherence rates to colonoscopy, positivity rates of relatives and discount rates.

A total of 40 families were studied. The total cost for Strategy 1 amounted to R4 932 718 ($332 617) compared to R390 308 ($26 319) for Strategy 2 (Discount rate 3%; Adherence 75% and Positivity rate of relatives 45%). Base case analysis indicated a difference of 92% less in the total cost for Strategy 2 compared to Strategy 1. Univariate sensitivity analyses showed that the difference in cost between the two strategies was not sensitive to changes in discount rates, adherence rates or positivity rates of relatives.

Compared to colonoscopy screening only, colonoscopy combined with genetic testing presented a less costly option by identifying patients at high risk of colorectal cancer for screening. Testing of relatives should be facilitated since, compared to probands, genetic testing of relatives is less costly and is likely to have more benefit. Effectiveness of the screening programmes should be established through further research.

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Abbreviations and Acronyms

BAS	Basic Accounting System
CBA	Cost benefit analysis
CEA	Cost effective analysis
CRC	Colorectal cancer
CSIR	Council for Scientific and Industrial Research
CUA	Cost utilisation analysis
DBSA	The Development Bank of South Africa
DNA	Deoxyribonucleic acid
DOH	Department of Health
DPSA - COLA	Department of Public Service and Administration – Cost of Living Adjustments
EPCAM	Epithelial cell adhesion molecule
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
FDR	First degree relative
FOBT	Faecal occult blood test
GSH	Groote Schuur hospital
HTA	Health Technology Assessment
HREC	Human Research Ethics Committee
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
LS	Lynch Syndrome
MLH1	MutL homologue 1
MLPA	Multiplex ligation-dependent probe amplification
MSH2	MutS homologue 2
MMR	Mismatch repair
MSH6	MutS homologue 6
MSI	Microsatellite instability
NDOH	National Department of Health
NHLS	National Health Laboratory Services
NGS	Next-generation sequencing
PCR	Polymerase chain reaction
PMS2	Postmeiotic segregation increased 2
QUALY	Quality adjusted life years
UCT	University of Cape Town

Glossary

BRAF V600E	A *BRAF* gene mutation identified in a number of cancers, including colorectal cancer.
Incremental cost-effectiveness ratio	In a specific population, the difference in the average cost of two interventions divided by the difference in the average outcomes of the two interventions.
Predictive testing	Testing for a mutation that is known.
Proband	The first medically identified individual in a family affected with a disorder and serves as the starting position for the genetic study of the family.
Sporadic colorectal cancer	Colorectal cancer that does not appear to have an hereditary feature.
Polymerase chain reaction (PCR)	A method used to amplify DNA sequences.
First degree relative	A relative that is a parent, sibling or child

PART A: PROTOCOL

A comparative cost analysis of two screening strategies for colorectal cancer in Lynch Syndrome in a tertiary hospital, South Africa

1. Background and rationale

1.1 Background

Lynch Syndrome is clinically defined as a disorder that predisposes individuals to colorectal cancer, endometrial cancer and certain other cancers as a result of an underlying germline mismatch repair (MMR) gene mutation (Vasen et al. 2013). The disorder presents with high rates of multiple primary tumours, has an early age of onset and generally has an absence of typical risk factors (Vasen et al. 2013). Carriers of a mutation in any of the mismatch-repair (MMR) genes have a lifetime risk for colorectal cancer of 25% to 75%, compared to a lifetime risk 5% in the general population (Giardiello et al. 2014; Snowsill et al. 2014; Vasen et al 2013). Lynch Syndrome includes individuals with existing cancers as well as those who have not yet developed cancer (Palomaki et al. 2009).

Worldwide, colorectal cancer is noted as the third most common cancer and cause of cancer-related deaths (Graham et al. 2012). In 2008, colorectal cancer accounted for more than 600 000 deaths of which 70% occurred in low and middle income countries (Graham et al. 2012). In South Africa, colorectal cancer is the fifth most common cancer, with approximately 4 697 new cases and 3 138 deaths reported in 2012 (National Health Laboratory Services: Globocan, 2015). Just over 50% of the new cases diagnosed and 41% of deaths were in persons less than 65 years old (Globocan 2015). The most common cause of hereditary colorectal cancer is Lynch Syndrome which accounts for approximately 3% to 5% of all colorectal cancers (Bonadona et al. 2011; Snowsill et al. 2014). Other than the Lynch Syndrome register maintained by the University of Cape Town (UCT), there are few hereditary colorectal cancer registers in South Africa (Coetzee et al. 2013). To date, this register has recorded 61 families who mainly live in the Western Cape and Northern Cape areas (Voster, A: Division of Human Genetics: UCT, personal communication 2015).

1.2 Problem Statement

Individuals with Lynch Syndrome have an elevated risk for developing cancer, with the highest risk for colorectal cancer (Snowsill et al. 2014). Estimated lifetime risks for colorectal cancer of 25% to 75% have been reported in many studies (Snowsill et al. 2014). Progression of adenoma to carcinoma is approximately five times more accelerated in individuals with Lynch Syndrome compared to sporadic and familial colorectal cancers (Snowsill et al. 2014; Vasen et al. 2013). Furthermore, colorectal cancer is generally asymptomatic until it has reached an advanced stage. For these reasons an effective screening programme is fundamental for early detection and successful management of colorectal cancer (Snowsill et al. 2014 & Vasen et al. 2013).

Colonoscopy is the only screening programme that has proved to be effective for these individuals (Palomaki et al. 2009; Giardiello et al. 2014; Snowsill et al 2014). Two main advantages of appropriate screening are the early detection of cancer and consequently improved chances of curative treatment and secondly, the early detection of pre-cancerous lesions which allows for removal of the polyps before it progresses to cancer. Studies have shown that effective colonoscopy screening programmes reduced mortality by 65% to 72% (Palomaki et al. 2009; Giardiello et al. 2014; Snowsill et al 2014). Stupart et al. (2009) showed an 80% decrease in mortality in a South African study.

Though sufficient evidence exists of the valuable benefits, formal colonoscopy screening programmes do not exist for individuals with Lynch Syndrome in South Africa (Thomson, S: Gastroenterology clinic: Groote Schuur hospitals, personal communication 2015). Public sector colonoscopy services, that service approximately 80% of the country's population, are few and predominantly limited to secondary and tertiary level care. Colonoscopies are performed by medical or surgical gastroenterologists only, which contributes to the high cost

of the service. Due to the limited professional skills and services available, colonoscopies are generally not provided for screening purposes, but are performed on patients that already present with symptoms in order to exclude cancer (Thomson, S: Gastroenterology clinic: Groote Schuur hospitals, personal communication 2015).

In a resource constrained environment, accurate prediction of individuals at high risk of colorectal cancer who will benefit from colonoscopy screening and leaving those at low risk of disease unexposed to potentially invasive screening procedures, will reduce the burden on services as well as optimise the use of scarce resources (Snowsill et al. 2014). Genetic testing is the only method to confirm a diagnosis for Lynch Syndrome and evidence suggested that it is a cost-effective and reliable strategy to identify individuals for colonoscopy screening (Snowsill, et al. 2014). Furthermore, genetic testing combined with immunological testing is the preferred strategy in terms of cost-effectiveness (Palomaki et al 2009; Mvundura et al. 2010; Ladabaum et al. 2011; Snowsill, et al. 2014). The genetic testing service available for testing for Lynch Syndrome in patients from this study was provided on a research basis by the Human Genetics Research Unit in the Division of Human Genetics at the University of Cape Town (Ramesar, R: Division of Human Genetics: UCT, personal communication 2015).

The lack of genetic testing and colonoscopy screening programmes pose a major drawback for the management of colorectal cancer in individuals with Lynch Syndrome. Determining the costs of providing these services is one of the key initial steps to assessing affordability and successful implementation of such services.

1.3 Rationale and justification of study

Apart from the high risk rate associated with colorectal cancer in LS, these cancers occur, generally, before the age of 50 years with numbers beginning to increase noticeably from the

age of 30 years (Bonadona et al. 2011; Cohen et al. 2014; Snowsill et al 2014). This age range includes persons that are financially independent, economically active and support families. Preventing or delaying cancer onset, by appropriate screening strategies, would have health related, social and economic benefits for the country. It is, therefore, important to establish the cost of colonoscopy screening options as this would contribute to assessing affordability of such services to the health service provider.

Colonoscopy screening and clinical genetics have a strong emphasis on early detection and prevention of cancers which is in line with the National Department of Health's strategic objective of enhanced wellness through primary, secondary and tertiary prevention (Department of Health: Western Cape. 2014). Also, the Western Cape Department of Health issued a genetic services policy framework for the province (Department of Health: Circular H212/2014). Services listed within the packages of care included genetic risk based on family history for e.g. cancers. The policy further specified the development of a "Rare Disease Policy" which should address the equitable rationing of scarce resources (Department of Health: Circular H212/2014). Results from this study would contribute to this policy by informing on the resource allocations and affordability of an effective Lynch Syndrome genetic testing programme.

No published study has assessed the cost implications associated with providing a formal public sector colonoscopy and genetic testing screening service for patients with Lynch Syndrome in South Africa. Evidence with regards to screening strategies for Lynch Syndrome suggested that targeted screening is cost-effective as opposed to no screening (Snowsill et al. 2014). Almost all of these studies were conducted in high income countries and generalisability to the South African context is impractical as cost-effectiveness is largely context specific and linked to available resources and practices. (Buchanan et al 2013; Gray et al. 2012; Drummond et al. 2005; Snowsill et al 2014).

This study, therefore, aims to collect and analyse primary data specific to the South African context in order to compare the cost implications of two screening options from a provider's perspective; i.e. colonoscopy screening for all Lynch Syndrome-suspected individuals versus targeted colonoscopy screening for the individuals diagnosed with Lynch Syndrome after genetic testing. Based on literature (Snowsill et al. 2014), it is hypothesised that targeted colonoscopy screening will reduce the number of patients requiring colonoscopy and will, thus present a less costly option.

1.4 Literature review

1.4.1 Lynch Syndrome

Lynch Syndrome (LS) is an autosomal dominant disorder that predisposes individuals to cancers, especially colorectal cancer (Cohen et al. 2014). A defect in the MMR system leads to loss of function of the entire MMR complex and an inability to restore base-base mismatches and small insertions and deletions in DNA sequences. This results in an accelerated accumulation of genetic mutations which often progresses to cancer. Mutations were found in one of the four MMR genes, *MLH1, MSH2, MSH6* or *PSM2*. More recently, deletions of the 3' end of *EPCAM* were reported and these deletions resulted in epigenetic hypermethylation of the *MSH2* promoter, thereby resulting in LS (Cohen et al. 2014).

The risks of developing cancers associated with LS are continuing to evolve with the increased application of germline testing and these risks are highly MMR gene mutation and sex dependent (Snowsill et al. 2014; Cohen et al. 2014). For men the risk of colorectal cancer was reported to be higher than for women (38% - 45% vs 31% - 35%) (Bonadona et al. 2011; Giardiello et al. 2014). The highest risks, in the region of 40% to 70%, are associated with individuals with *MLH1* and *MSH2* mutations, with lower risks reported for *MSH6* (10% - 22%) and *PMS2* (15% - 22%) (Bonadona et al. 2011; Steinke et al. 2013;

Vasen et al. 2013; Giardiello et al. 2014). *MHL1* and *MSH2* mutations were identified in the cohort recorded on the UCT DNA database, but to date no *MSH6, PMS2* and *EPCAM* mutations were identified (Voster, A: Division of Human Genetics: UCT, personal communication 2015). The MMR mutation distribution in the UCT cohort indicates a population that falls in the highest risk category, reinforcing the need for an effective screening programme.

Unlike sporadic cancers that generally occur approximately after the age of 60 years, LS-associated colorectal cancers have an earlier onset, i.e. < 50 years old, and may occur as early as 25 years of age (Giardiello et al. 2014; Cohen et al. 2014; Vasen et al. 2013). The estimated cumulative risk in carriers was shown to increase from the age of 30 years irrespective of the gene mutation (Bonadona et al. 2011). Around 15% - 20% of cancer survivors with LS will develop a second colorectal cancer within 10 years, 40% - 50% within 20 years and >60% within 30 years (Cohen, et al. 2014). In LS, polyps may progress to carcinoma within 2 to 3 years as opposed to 8 to >10 years in the general population. For these reasons, evidenced-based guidelines recommend colonoscopy every 1 to 2 years as opposed to every ten years as per the general population (Cohen, et al. 2014; Snowsill et al. 2014; Giardiello et al. 2014; Vasen et al. 2013).

1.4.2 Diagnosis and screening of Lynch Syndrome

Diagnosis of Lynch Syndrome has progressed over the past two decades to include family history, histopathological characteristics and germline testing (Cohen et al. 2014).

Though family history is an important element in assessing risk in the general population, neither the Amsterdam criteria nor the Bethesda criteria delivers the necessary sensitivity and specificity as a preliminary screening test (Vasen et al. 2013; Giardiello et al. 2014). Faecal occult blood tests (FOBTs) detect mainly asymptomatic cancers by detecting blood

from bleeding cancers (Coetzee 2013). Sensitivity of a single FOBT is about 30% as cancers bleed intermittently. Although cheap and non-invasive, the low sensitivity of FOBT is not ideal for screening for LS. Flexible sigmoidoscopy is less demanding technically and less invasive than colonoscopy and does not require full bowel preparation. This procedure allows for visualisation, removal of polyps and tissue biopsy of the left colon. However, about two thirds of LS-associated colorectal cancers appear proximal to the left colon and may be missed with sigmoidoscopy (Coetzee 2013).

Colonoscopy allows for inspection of the entire colon and, if performed by a skilled professional, provides a sensitivity of up to 100% for detecting cancers and advanced adenomas (Coetzee 2013). There are no randomised controlled studies on routine colonoscopy screening (Coetzee 2013; Palomaki et al. 2009; Snowsill et al. 2014). However, observational studies (Level IIb evidence) exist that indicated a 62% reduction in incidence of colorectal cancer and 65% - 70% decrease in mortality (Palomaki et al. 2009). A South African study showed that colonoscopy screening produced better outcomes compared to no screening i.e. 11% vs 27% for colorectal cancer diagnosis and 2% vs 12% for death from colorectal cancer, respectively (Stupart et al. 2009). Colonoscopy is more invasive, requires sedation and bowel preparation, and has morbidity associated with this procedure (Coetzee 2013; Snowsill et al. 2014). The most common, serious adverse events related to colonoscopy in the general population are death 0.08/1000, perforation (3.3/1000) and bleeding (11.1/1000) (Palomaki et al. 2009).

Cost-effectiveness studies have recommended genetic testing as a strategy to identify high risk individuals for colonoscopy screening (Palomaki et al. 2009; Snowsill et al. 2014; Vasen et al. 2013). Germline testing is performed on blood and is diagnostic for LS. Partial reflex testing is done i.e. the result of a test done will determine whether another test will be performed and which test will be performed. Microsatellite Instability testing (MSI) or

Immunohistochemistry (IHC) was indicated as the preferred preliminary test to identify patients for genetic testing. IHC has the added advantage of directing germline testing to one of the four MMR genes (Palomaki et al. 2009; Snowsill et al. 2014; Vasen et al. 2013). MSI testing is labour intensive and expensive (Coetzee 2013). Performing *BRAF* testing on tumours with absent *MLH1* staining would identify patients that would not benefit from *MLH1* gene sequencing and, consequently, significant cost savings could be implicated. (Palomaki et al. 2009; Snowsill et al. 2014; Vasen et al. 2013). Locally, however, *BRAF* testing is technically not feasible (Voster, A: Division of Human Genetics: UCT, personal communication 2015). Recommendations on the most cost-effective germline testing have not yet been determined (Giardiello et al. 2014; Hampel 2010). Genetic testing counselling is recommended before and after undergoing germline testing, as well as follow-up counselling during colonoscopy screening sessions (Giardiello et al. 2014; Hampel 2010; palomaki et al 2009).

1.4.3 Cost effectiveness studies on screening strategies for Lynch Syndrome

Research to date, on cost-effectiveness of screening strategies for Lynch Syndrome, has focused on high income countries and therefore generalisability to the South African population is problematic.

A recent Health Technology Assessment included a systematic review of 32 cost-effectiveness studies (Snowsill et al. 2014). Most of the studies were conducted from a health provider perspective and the majority of studies were set in the United States of America. Studies in the review used different tests or combination of tests, and therefore it was not possible to identify the most frequently used tests. Many of the studies did not meet the criteria from the Drummond checklist (Drummond et al. 2005). The review failed to provide consistency with regards to the strategies or tests that would be most cost-effective.

All studies, however, concluded that screening for Lynch Syndrome compared to no screening was cost-effective (Snowsill et al. 2014).

Snowsill et al (2014) further conducted an economic evaluation comparing 8 screening strategies. Compared to no testing as the base case, MSI + *BRAF V006* + genetic testing produced the lowest ICER. The more tests that were performed in sequence, the greater the specificity as well as the increased costs. Sensitivity analysis indicated that, even at low rates of acceptance of diagnostic tests and genetic counselling, Lynch Syndrome testing is cost-effective compared to no testing. Sensitivity analysis performed on widely varying the number of relatives per proband, including no relatives, found screening for Lynch Syndrome more cost-effective than no screening. The majority of the diagnosing cost for the cohort was due to diagnosing the probands, as opposed to diagnosing the relatives. Costs were driven by the number of tests taken. Long term, the most influential cost driver was the cost of colonoscopies and diagnostic costs did not significantly influence the variation in costs between strategies. Preventative costs outweighed the increased savings in cost from colorectal treatment (Snowsill et al. 2014).

Table 1 reflects the costs reported in various cost-effectiveness studies performed in different countries (Gross 2015).Total screening costs were around $2 242 to $3 345. One study was unusually high at a total cost of $6 312. Generally, the largest contributors towards the screening costs were the genetic testing for MLH1 and colonoscopy. Long-term the colonoscopy cost will be the main cost driver as the other costs are once-off costs. The lowest cost contributors were the genetic counselling costs and approaching relatives. The predictive tests for relatives were in all cases significantly lower than the genetic sequencing for MLH1 (identifying the mutation). This indicates the value of identifying a family mutation – i.e. relatives may be identified at a much lower cost for genetic testing and may benefit more from colonoscopy screening as they may not have cancer yet as opposed to the

proband who often present with cancer already. Furthermore, the cost of excluding a relative that tested negative for a mutation is far less than the cost of lifetime colonoscopy screening.

Table 1: Base case estimates of costs of routine testing and colonoscopy for Lynch Syndrome in patients with colorectal cancer and first degree relatives, in 2014 US $

Study	Pre-test counselling	Post-test counselling	Counselling for gene sequencing	IHC	Gene sequencing for *MLH1*	Approaching relatives	Test for relative (predictive)*	Combined test and counselling	Colonoscopy unit cost	TOTAL COST
Mvundura et al. (2010) USA	22	106	194	290	899	350	61	441	1043	3345
% of total cost	0.66	3.17	5.80	8.67	26.88	10.46	1.82	13.18	31.18	100
Ladabaum et al (2011) USA	NR	112	198	300	942	118	492	610	690	2970
% of total cost	NR	3.77	6.67	10.10	31.72	3.97	16.57	20.54	23.23	100
Sie et al (2007) Netherlands	25	136	0	184	1184	77	353	430	206	2242
% of total cost	1.12	6.07	0	8.21	52.81	3.43	15.74	19.18	9.19	100
Snowsill et al (2014; 2015) UK	0	0	103	366	714	103	265	368	911	2565
% of total cost	0	0	4.02	14.27	27.84	4.02	10.33	14.35	35.52	100
Severin et al (2014) Germany	57	161	0	166	5268#	57	281	338	265	6312
% of total cost	0.90	2.55	0	2.63	83.46	0.90	4.45	5.35	4.20	100
Barzi et al (2015) USA	NR	112	198	300	942	118	492	610	690	2970
% of total cost	NR	3.77	6.67	10.10	31.72	3.97	16.57	20.54	23.23	100

NR: Not reported * Not added to total (included in combined counselling and test)
Genetic testing costs is not higher in Germany. The German reimbursement for gene sequencing is an outlier.

Adapted from Grosse 2015. *Healthcare.* 3, 860-878.

2. Aims, objectives and conceptual framework

2.1 Aim

The aim of the study is to provide evidence of the relative cost of two screening options for colorectal cancer for persons with Lynch Syndrome for policy-making purposes in the public sector. Thus, costs for colonoscopy screening only (Strategy 1) will be compared with costs of conducting genetic testing for Lynch Syndrome followed by colonoscopy screening for the individuals that tested positive for Lynch Syndrome (Strategy 2).

2.2 Objectives

1. To estimate the unit cost of colonoscopy.
2. To estimate the weighted average unit cost of identifying the MMR gene mutation in patients with colorectal cancer.
3. To estimate the weighted average unit cost of genetic testing for relatives of the proband.
4. To use these unit costs to estimate and compare the total cost of screening for the two screening strategies for the same cohort of individuals.

2.3 Conceptual framework

Unit costs for colonoscopy and genetic testing will be estimated according to the utilisation patterns at the health facility and the expenditure incurred. Unit costs for colonoscopy will be estimated by dividing the total annual cost of colonoscopy by the number of colonoscopies performed per annum. Unit costs for genetic testing will be estimated by calculating the weighted average unit cost for genetic testing where the weighting will be estimated according to the proportion of patients that required a particular test or series of tests. These unit costs will be applied to the actual utilisation of potential LS patients (probands) and the total number of colonoscopies estimated per individual per lifetime per Strategy option in order to estimate the total costs for Strategy 1 and 2. Table 2 presents the conceptual framework for Strategy 1 and 2.

Table 2: Conceptual framework for estimating costs per screening strategy

STRATEGY 1 Colonoscopy screening only	STRATEGY 2 Genetic testing and colonoscopy screening for positively tested individuals
1. Unit Cost: To estimate the unit cost of colonoscopy. **2. Utilisation**: To estimate the total number of colonoscopies required per lifetime for all individuals eligible for colonoscopy as per Strategy 1. **3. Total cost = Unit cost x Utilisation:** To estimate the total cost of screening for Strategy 1 (i.e. unit cost of colonoscopy x total number of colonoscopies required).	**1. Unit Cost A:** To estimate the unit cost of colonoscopy. **2. Utilisation A:** To estimate the total number of colonoscopies required per lifetime for all individuals eligible for colonoscopy as per Strategy 2. **3. Unit Cost B**: To estimate the weighted average unit cost for: - genetic testing for diagnosing a proband - genetic testing for diagnosing a relative - genetic counselling **4. Untilisation B:** To estimate the total number of tests and genetic counselling sessions required. **5. Total cost = (Unit cost A x Utilization A) + (Unit cost B x Utilisation B):** To estimate the total cost of screening for Strategy 2 (i.e. unit cost of colonoscopy x total number of colonoscopies required + unit cost of genetic testing x total number of tests + unit cost of genetic counselling x total number of counselling sessions required).
6. To compare the total cost of Strategy 1 and 2	

3. Method

3.1 Study design

The study design will be a comparative cost analysis, focusing on the collection of primary cost data, and will be conducted from a service provider perspective. A predominantly micro-costing, ingredient-based approach will be followed. The most relevant costs will be related to the resources used to perform colonoscopy and genetic testing. Costs of resources will be presented in 2016 South African rands and US dollars.

3.2 Setting and population

The study will be undertaken at Groote Schuur hospital (GSH) in Observatory in the Western Cape, South Africa. GSH is a public sector, tertiary, academic hospital that provides sub-specialist level care. In South Africa, approximately 80% of the population seeks health care in the public sector (Department of Health 2014) and patients in this study were predominantly from the Western Cape and Northern Cape provinces. The colonoscopy service was provided by GSH while the genetic testing service for testing for Lynch Syndrome was provided on a research basis by the Human Genetics Research Unit in the Division of Human Genetics at the University of Cape Town (Ramesar, R: Division of Human Genetics: UCT, personal communication 2015).

Patients on the UCT Lynch Syndrome DNA database (Ethics approval: HREC REF: 217/2010) will be considered in the study (Voster, A: Division of Human Genetics: UCT, personal communication 2015). The patients (probands) on this database were selected if they met the Revised Bethesda Criteria after presenting with colorectal cancer or other LS-related cancer. Due to advancements in genetic testing over the years, analysis of the data will be restricted to probands tested between 01 November 2014 and 30 October 2015 in order to ensure that the latest test methods are assessed to estimate costs. Probands and their relatives will be analysed according to their age, relationship to the proband, alive status, tests performed, results of tests and surgical procedures performed. Probands and their first degree relatives (parents, children and siblings) that are eligible for colonoscopy screening will be considered for inclusion in the cost assessment. Persons that would not be eligible for colonoscopy screening would be excluded from the study, such as spouses, spouse's family, deceased persons, persons under 25 years and over 60 years and persons that would not have colonoscopy screening (e.g. patients who had total colectomies). See Part D: Appendices: S1 Fig. and S2 Fig.)

3.3 Screening strategies

The screening strategies considered were based on the services currently available at GSH and the collaboration with the Division of Human Genetics at UCT. Probands and first degree relatives will be considered as per the proposed protocol and current services available (Ramesar, R: Division of Human Genetics: UCT, personal communication 2015). LS-associated mutations have an autosomal dominant pattern and, therefore, there is a 50% chance that the mutation will be passed on to the first degree relative.

Both screening strategies will be applied to the same cohort (see section 3.2 for inclusion and exclusion criteria) and total cost per strategy will be estimated. Thus, probands on the DNA database that were tested between 01 November 2014 and 30 October 2015, and their first degree relatives will be evaluated according to the two strategies below (See Part D: Appendices S1 Fig and S2 Fig):

- Strategy 1 will involve estimating the cost for intensive colonoscopy screening for probands and their first degree relatives that are eligible for screening.

- Strategy 2 will involve estimating the cost for genetic testing for all probands and the first degree relatives of LS-positive probands plus the cost of intensive colonoscopy screening for all individuals with a genetic test-confirmed diagnosis of Lynch Syndrome.

Intensive colonoscopy screening involves colonoscopy screening biennially for patients under 30 years old and annually for individuals aged 30 years and older up to 60 years; thereafter colonoscopy will be every ten years (Voster, A: Division of Human Genetics: UCT, personal communication 2015). Individuals that tested negative on germline testing will be managed as per the general population i.e. colonoscopy every ten years after the age of 50 years. Taking into account the ages of the probands and their first degree relatives, the total lifetime number of colonoscopies for the two strategies will be estimated and costed.

Colonoscopy is a 30 to 60 minutes procedure performed in a dedicated, equipped room (Algar: GSH, personal communication 2015). A colonoscope is inserted into the rectum, through the colon and as far as the caecum. Prior to the procedure, patients are given a special cleansing preparation to clear the bowel. Sedatives may be given for pain control and to relax the patient. An intravenous cannula is prepared in the event that patients may require intravenous fluid or medication. The patient's heart rhythm and blood pressure is monitored continuously. Post-colonoscopy, the patient is kept in an observation area for 1 to 2 hours. In the event of an incomplete colonoscopy, the procedure may be repeated at a later stage. (Algar: GSH, personal communication 2015)

Genetic testing to diagnose Lynch Syndrome is complex due to the genetic heterogeneity and the preliminary screening tests that can be performed prior to genetic testing (Hampel 2010). The reflex genetic testing procedure followed by the Division of Human Genetics at UCT for diagnosing Lynch Syndrome was applied in this study. (Voster: Human Genetics: UCT, personal communication 2015). Where possible, immunohistochemistry (IHC) testing is routinely performed as a first line preliminary screening test (Coetzee 2013). Negative staining of IHC testing i.e. absence of an MMR gene product, suggests a high risk for Lynch Syndrome. If the IHC shows presence of all genes, but a strong clinical suspicion exits, the patient will be offered MSI testing. MSI testing is expensive, labour intensive, time consuming and requires a skilled geneticist and, therefore, is only provided on request (Coetzee 2013). IHC and MSI are provided by the National Health Laboratory Services (NHLS). Germline testing is provided via NHLS and Division of Human Genetics Department at UCT (Voster: Human Genetics: UCT, personal communication 2015). All patients (probands) on the database undergo genetic testing. Genetic testing involves DNA isolation from whole blood, followed by testing for the 5 common founder mutations. A positive result for a founder mutation would be followed by Multiplex Ligation-dependent Probe Amplification (MLPA) analysis or Sanger sequencing on a different day and different

blood sample for quality assurance (confirmation) purposes. In the case of a known mutation, that is not a common founder mutation, Sanger sequencing would be done, and this would be repeated on a separate day on a separate blood sample for quality assurance purposes. On identification of the MMR gene mutation in the index patient, the relatives would be offered germline testing for the identified MMR mutation. *BRAF V600E* is not offered due to its technical complexity. Individuals identified for genetic testing should receive genetic counselling by a trained genetic counsellor prior to and post undergoing genetic testing, as well as during colonoscopy screening. In addition, informed consent for genetic testing is a prerequisite to genetic testing. All positive probands and their first degree relatives would be offered intensive colonoscopy screening (Voster: Human Genetics: UCT, personal communication 2015; Hampel 2010).

In summary, IHC is performed on probands with suitable colon tissue available for this test. All probands would receive screening genetic tests i.e. the Common Founder test or a Sequencing test for those with a known family mutation that is not a founder mutation. Only probands with positive screening tests would receive quality assurance / confirmatory tests i.e. a digestive test and / or another sequencing test. See Part D: Appendices: S3 Fig for the flow diagram of tests performed.

3.4 Cost analysis

Costs are the value of the resources required to provide a particular service (Gray et al. 2012). The costs for performing a colonoscopy and genetic testing will be identified, quantified (measured) and valued.

Table 3 displays a summary of the categories of costs / resources that will be considered, together with the methods that will be used to collect, measure and value these costs.

Table 3: Identification, measurement and valuation of costs

TYPE OF COST	IDENTIFICATION	MEASUREMENT		VALUATION	
Capital cost	**Categories**	**Costing method**	**Source of data**	**Valuation method**	**Source of data**
Building	Colonoscopy room, recovery, consulting room, waiting room, toilet, prep room, laboratory space, laboratory extraction room, etc.	Proportion of square metres floor space used or proportion of activities	Observation and WCGH: Depart of Public Works architectural drawings	Replacement and contract prices or rent	NDOH/CSIR/DBSA Estimator; building contractors for laboratory
Equipment	Medical & genetic testing equipment, , heart monitor, colonoscope, processor, gel documentation, workstation, computer, thermal cycler, centrifuge, refrigerators, other laboratory equipment	Proportion of lifetime use or number of uses / activities.	Observation and staff interviews; Asset report	Replacement and contract prices	WCGH: Depart of Public Works, WCGH SCM records and contracts, UCT expenditure records, commercial price lists
Furniture	Tables, chairs, cabinets, examination beds, stools, bed steps, etc.	Proportion of lifetime use	Observation and staff interviews; Asset report	Replacement and contract prices, rental fees	WCGH Depart of Public Works, WCGH SCM records and contracts
Recurrent cost	**Categories**	**Costing method**	**Source of data**	**Valuation method**	**Source of data**
Personnel	Administration, clinician, nurses, managers, genetic counsellors, laboratory technicians, medical technician, general assistants	Proportion of working hours spent on colonoscopy, genetic testing or counselling	Observation and staff interviews	Gross salary per month, including benefits (Cost to company)	WCGH PERSAL report, government salary packages (DPSA COLA); GSH personnel report
Overheads and Maintenance	Overhead (electricity, telephone, stationery, water, laundry, etc.). Maintenance of equipment, waste disposal, housekeeping	Proportion of personnel time; proportion of floor space; 8% markup for maintenance	Observation, staff interviews	Tender contract prices and expenditure records	WCGH Department of Public Works, GSH BAS (financial) reports, WCGH SCM records & contracts, UCT expenditure records
Consumables	Needles, syringes, gloves, swabs, specimen jars, cleaning supplies, disinfectants, aprons, stationery, polypectomy snares, forceps, needle injector, plates	Shared -proportion of patients Not shared- quantity consumed	Procurement records, observation, patient records	Tender contracts and expenditure records	WCGH SCM records and contracts; GSH ward procurement records
Medicines	Sedation, premed, bowel preparation, IVI fluids, etc.	Shared -proportion of patients Not shared- quantity consumed	Observation and patient records	Tender contract prices and expenditure records	WCGH SCM records & contracts; NDOH Pharmaceutical contracts; GSH pharmacy records
Laboratory tests	Laboratory tests, genetic tests, DNA isolation, MSI test, IHC test, disinfectants, reagents, etc.	Shared -proportion of patients Not shared- quantity consumed	Procurement records, observation and patient records	Tender contract prices and expenditure records	WCGH SCM records, BAS report, contracts, NHLS, UCT procurement records & finance report, suppliers' price list

BAS: Basic Accounting System; CSIR: Council for Scientific and Industrial Research; DBSA: The Development Bank of South Africa; DPSA- COLA: Department of Public Service and Administration Cost-of-Living Adjustments; GSH: Groote Schuur hospital; IHC: Immunohistochemistry; MSI: Microsatellite Instability; NDOH: National Department of Health; NHLS: National Health Laboratory Services; PERSAL: Personnel and Salary System; WCGH: Western Cape Government – Health; WCGH SCM Supply Chain Management; UCT: University of Cape Town

Costs will be estimated in terms of recurrent costs and capital costs. Recurrent costs will generally be estimated by using an ingredient-based approach i.e. costs will be calculated by multiplying unit costs by the quantities or proportion of resources used. Any item used for longer than one year will be considered a capital cost (Gray et al. 2012). The equivalent annual cost of a capital item will be estimated by annuitizing the initial capital expenditure using a discount rate of 3% (Glick et al. 2007; Mangham 2009; Drummond et al. 2005). Useful life-years for capital items will be assumed as follows - buildings: 30 years; major equipment: 5 to 10 years; furniture: 10 years; vehicles: 3 – 5 years and small equipment: 1 – 5 years; training: 10 years (Drummond et al. 2005; Somda et al. 2007). An 8% mark-up is the standard included in Department of Health contracts for the maintenance of equipment and will be considered for calculating maintenance costs of equipment. (Rademeyer: Deputy Director: WCGH Department of public Works, personal communication 2015).

For shared costs e.g. overheads, departments or resources that directly affect the service to the patient will be identified. A unit of output e.g. number of hours for staff costs, square meters floor space for housekeeping, etc. will be determined and allocation of costs will be done in terms of the proportion of units of outputs used to provide the service. (Drummond et al. 2005; Gray et al. 2012).

For personnel costs, a unit cost (cost per minute) for the different cadre of staff will be determined by dividing the annual total cost to company by the annual total working minutes of the staff member.

Major adverse events are rare (Palomaki et al. 2009) and will be excluded from the study. Grosse (2015) reported in a review that differences in assumptions regarding complications as well as excluding complications had little influence on incremental cost effectiveness ratios (ICERS).

Data from colonoscopies performed on the study cohort indicated that approximately 6% of colonoscopies may require repeat colonoscopies (Algar: GSH, personal communication 2015). Repeat colonoscopies will be included in the average unit cost for colonoscopy.

The cost of genetic testing may vary from patient to patient depending on the type of test and the number of tests that were conducted on the patient. The unit cost for genetic testing per proband or first degree relative will, therefore, be estimated by calculating the weighted average cost for genetic testing where the weighting will be estimated according to the estimated proportion of patients that required a particular test or series of tests. Costs for tests performed by the NHLS (e.g. IHC and MSI) will be obtained from expenditure reports from Groote Schuur hospital or from the NHLS price lists.

Discount rate should be applied for programmes with differential timing of cost outlays. A discount rate of 3%, consistent with existing literature, was used as per the recommendations by Drummond et al, 2005. The South African Department of Health recommends that undiscounted costs should be reported on as well as a baseline annual discount rate of 5% (Department of Health; Government Gazette No. 36118). Thus, sensitivity analysis was done on discount rates of 0% and 5%.

The unit cost data of colonoscopy and genetic testing, as well as the total lifetime number of colonoscopies required will be used to estimate the total cost for the cohort for Strategy 1 and Strategy 2.

Data will be collected in 2015 by interviewing staff, folder reviews and observing activities. Costs will also be obtained from expenditure records, tender documents, purchase contracts, service agreements and the Department of Health (DOH) financial year 2014/2015 expenditure records and UCT 2015 expenditure and financial records. DOH costs will be used to value resources and where not available, market prices will be used. In the case of donated / volunteer resources, costs of these resources will be valued in terms of DOH costs,

and if not available, the market prices (or actual cost) will be used (Drummond et al. 2005; Gray et al. 2012). Examples of data collection and analysis tools are shown in the appendices (See part D: Appendices: S1 Table to S4 Table).

3.5 Sensitivity analysis

Uncertainties that would be most relevant in the study include the number of first degree relatives that would test positive and the number of colonoscopies required. The number of colonoscopies would depend on adherence to colonoscopy screening, and the number of relatives that tested positive. Literature reported adherence rates ranging from 79% to 88% (Grosse et al. 2015). However, a study conducted in South Africa found an adherence rate as low as 25% in LS-diagnosed persons (Bruwer et al. 2013). Therefore, adherence rates of 25%, 50%, 75% and 85% will be analysed. Positivity rates of 39% to 50% were reported in literature (Grasse et al. 2015). However, around 27% of the relatives on the DNA database tested positive. Sensitivity analysis will, therefore, be conducted on positivity rates of 30%, 45% and 50%. Drummond et al. 2005 recommended that sensitivity analysis be performed on discount rates used commonly as well as no discount rate. Thus, discount rate of 5% and 0% will be considered in the sensitivity analysis as per the recommendations in the South African Department of Health guidelines for pharmaco-economic submissions (Department of Health; Government Gazette No. 36118).

3.6 Assumptions

The following assumptions will be made:

- Mortality rates as per the general population were applied to both strategies. Risks of cancers that are part of the LS spectrum in this study population have not been published. The costs, therefore, may be overestimated. This exclusion is not expected to affect the direction of the hypothesis as the incidence of other cancers would be higher in the genetic tested LS-diagnosed group (Strategy 2) and thus potential increased mortality rate in this group.
- All probands and first degree relatives of positive probands will be willing to undergo genetic testing.

4. Data analysis and management

Costs will be estimated and presented as per the objectives in section 2.2: Aims and Objectives and section 3.4: Cost analysis. Data will be captured and analysed using Microsoft Excel®; and stored in password protected folders. Part D: Appendices: S1 Table to S4 Table shows examples of tools for data collection and calculations of costs for personnel, buildings, equipment and consumables; and Part D: Appendices: pages 3 – 5 illustrate the assessment of eligible individuals for colonoscopies and genetic testing. See section 2.3: Conceptual framework for estimation of unit costs and total costs for colonoscopy and genetic testing. Completeness and accuracy of the data is the responsibility of the researcher. A data back-up system will be maintained. Data from the templates will be recorded directly onto the database. The data will be cleaned and once all queries have been addressed, the database will be locked.

5. Ethical considerations

5.1 Potential benefits and risks

This study poses no potential risk or harm to the participant. This study is unlikely to benefit the individual participants directly. Important indirect benefits will be that the information may direct future resources towards the management of Lynch Syndrome in terms of genetic testing and colonoscopy screening, and prevention of inappropriate exposure to invasive colonoscopy procedures.

5.2 Autonomy and informed consent

Informed consent will be obtained from staff and informants that assist with information and access to documents related to costs. Informants and staff will be made aware that participation and withdrawal from the study is voluntary.

5.3 Confidentiality

Privacy and confidentiality will be assured. Information will be captured under unique identifiers and no names will appear on forms or in the database. No personal identifiers will be used in the analysis or appear in any publication or report. All electronic data will be password protected and accessible only to the study team. Paper forms will be stored in a locked cupboard.

5.4 Ethical approval

This protocol will be submitted to the University of Cape Town Human Research Ethics Committee (UCT HREC) for approval. The protocol will also be submitted to the relevant Provincial DOH authorities for review and permission to implement the study in areas of their jurisdiction.

6. Publication and dissemination

The study will be submitted for the Masters in Public Health: Health Economics degree. The findings of the study will also be submitted to the relevant Department of Health officials in the Western Cape, Division of Human Genetics: UCT, Groote Schuur hospital and persons that participated in the study. A manuscript will be drafted for publication.

7. Logistics

The study will be conducted over a 12 month period. The activities and time lines are shown in Table 4

Table 4: Study time lines

Activity	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec - Mar
Finalise protocol	X													
Obtain approval: GSH, DOH, Ethics	X													
Finalise data capture forms		X												
Collect data: Observation & interview		X	X	X	X									
Collect data: Review records, tender docs, etc.			X	X	X	X								
Capture data on database							X	X						
Analyse & clean data									X	X	X			
Write up												X	X	
Complete dissertation														X
Submission														X

8. Budget

The study will be self-funded.

References

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., et al. 2011. Cancer risks associated with germline mutations in *MLH1*, *MLH2* & *MLH6* genes in Lynch Syndrome. *JAMA.* 305:22, 2304-2310.

Bruwer, Z., Futter, M., Ramesar, R. 2013. A mobile colonoscopic unit for Lynch Syndrome: Trends in surveillance uptake and patient experiences of screening in a development country. *J Genetic Council*. 22: 125-137.

Buchanan, J., Wordsworth, S., Schuh, A. 2013. Issues surrounding the health economic evaluation of genomic technologies. *Pharmacogenomics*.14:15, 1833-1847.

Coetzee, E. 2013. Early detection of colorectal cancer. *CME*. 31:6, 210 – 212.

Coetzee, E., Thompson, S.R. 2013. Inherited colorectal cancer: A plea for a national registry. *SAJS*. 51:2, 42-43.

Cohen, S.A., Leininger, A. 2014. The genetic basis of Lynch Syndrome and its implications for clinical practice and risk management. *The Application of Clinical Genetics*. 7, 147-158.

Department of Health. 2013. Guidelines for pharmacoeconomic submissions. Government Gazette No. 36118. Pretoria: Government Printer

Department of Health: Western Cape Government. 2014. Annual performance plan 2014 / 2015. Cape Town: Department of Health.

Department of Health: Western Cape Government. 2014. Circular H212/2014: Genetic services policy framework. Cape Town: Department of Health.

Department of Health: Western Cape Government. 2015. Hospital fees: Revision of the Uniform Patient Fee Schedule (UPFS) in respect of externally funded, foreigners, revenue generation projects and patients treated by their private practitioner: Effective 1 April 2015. Finance instruction FAR:1/2015. Cape Town: Department of Health.

Drummond, M.F., Sculpher M.J., Torrance, W.G., Brien, J.B., Stoddard. G.L. 2005. *Methods for the Economic Evaluation of the Health Care Programmes.* New York: Oxford University Press.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. 2009. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine.* 1: 1, 35-41.

Giardiello, F.M., Allen, J.I., Axilbund, J.E., Boland, R., Burke, C.A., 4 , Burt, RW., Church, JM., Dominitz, J.A., Johnson, D.A., Kaltenbach, T., Levin, T.R., Lieberman, D.A., Robertson, D.J., Sapna Syngal, S., Rex, DK. 2014. Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US. Multi-Society Task Force on Colorectal Cancer. *The American Journal of Gastroenterology.* 147, 502-526.

Gray, A.M., Clarke, P.M., Wolstenholme, J.L., Wordsworth, S. 2012. *Applied Methods of Cost-effective Analysis in Health Care.* United Kingdom: Oxford University Press.

Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. 2007. Oxford, Oxford University Press.

Grosse, S.D., 2015. When is genetic testing cost-effective? Testing for Lynch Syndrome in patients with newly-diagnosed colorectal cancer and their relatives. *Healthcare.* 3, 860-878.

Hampel, H., 2009. Genetic testing for hereditary colorectal cancer. *Surg Oncol clin N Am.* 18:4, 678

Mangham, L. (2009) ACT Consortium Guidance on Economic Evaluation. Available at www.actconsortium.org/healtheconomicsguidance [20 July 2015]

National Health Laboratory Services. 2015. National Cancer Registry report 2009. National Institute for Occupational Health. http://www.nioh.ac.za [23 May 2015].

Palomaki, G.E., McClain M.R., Melillo, S., Hampel, H.L., Thibodeau, SN. 2009. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genetics in Medicine.* 11:1, 42-65.

Snowsill, T., Huxley, N., Hoyle, M., Jones-Hughes, T., Coelho, H., Cooper, C., Fraylin, I., Hyde, C., 2014. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. *Health Technology Assessment.* 18, 58.

Steinke, V., Engel, C., Büttner, R., Schackert, H.K., Schmiegel, W.H., Propping, P. 2013. Hereditary Nonpolyposis Colorectal Cancer (HNPCC) / Lynch Syndrome. *Dtsch Arztebl Int.* 110:3, 32-8.

Stupart, D.A., Goldberg, P.A., Algar, U., Ramesar, R. 2009. Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. *Colorectal Disease*. 11:2, 126-30.

Vasen, H.F.A., Blanco,I., Aktan-Collan, K., Gopie, J.P., Alonso, A., Aretz, S., Bernstein, I. (Mallorcca group). 2013. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut,* 62, 812–823.

Somda, Z.C., Meltzer, M.I., Perry, H.N. 2007. SurvCost 1.0: a manual to assist country and district public health officials in estimating the cost of the implementation of IDSRS. CDCP. Department of Health and Human Services. USA.

Wentink, M.Q., Räkers, M., 2010. Incidence and histological features of colorectal cancer in the Northern Cape Province, South Africa. *SAJS*. 48:4, 109-113.

PART B: STRUCTURED LITERATURE REVIEW

A comparative cost analysis of two screening strategies for colorectal cancer in Lynch Syndrome in a tertiary hospital, South Africa

1. Introduction

A comparative cost analysis will be conducted for screening options for colorectal cancer in Lynch Syndrome (LS), with a focus on the available options for South Africa. Objectives of this literature review will, thus, seek to inform on the following:

- An overview of LS and its impact within the South African context.
- Effective diagnosing and screening options for colorectal cancer in LS.
- Economic evaluation and cost implications of screening strategies for colorectal cancer in LS.
- Economic evaluation methodology for assessing costs, with a focus on screening strategies for colorectal cancer in LS.

This literature review, firstly, describes key aspects of Lynch Syndrome (LS) in terms of incidence, risks and clinical features of the disease in order to inform on the impact of LS on society. The next section briefly describes screening options for colorectal cancer in LS and this is followed by economic evaluations conducted on various screening strategies. Lastly, approaches to economic evaluations and cost analysis for priority setting and resource allocation in public health are discussed. The review concludes with describing the existing gaps in literature with regards to the purpose for this study.

A search filter was used to identify literature for in PUBMED, Google Scholar and the Cochrane Collaboration database. Search terms were based on search terms used in evidence-based guidelines and systematic literature reviews (Palomaki et al. 2009; Giardello et al. 2014; Snowsill et al. 2014). Search terms included Lynch Syndrome, health economics, cost analysis, cost-effectiveness, genomics, genetic testing, hereditary cancer, colorectal cancer, mismatch repair, MMR, HNPCC, hereditary nonpolyposis colorectal cancer, colorectal neoplasm, colonoscopy and colorectal cancer surveillance. Due to

advancements in technology and management of Lynch Syndrome, publications retrieved on these subjects were restricted to periods after 2004 (Palomaki et al. 2009; Giardello et al. 2014). The language filter was restricted to English publications. Four evidence-based guidelines (Palomaki et al. 2009; Giardello et al. 2014; EGAPP 2009; Vasen et al 2013) and one Health Technology Assessment (HTA) (Snowsill et al. 2014) formed the bases of the review. The information across these documents was generally consistent in terms of prognosis, risks, guidelines and similar studies were cited. Stupart et al (2009) provided observational study data on outcomes of colonoscopy surveillance for the population of this study. All studies on outcomes of colonoscopy were observational. Information on costs was contained in observational studies on cost-effectiveness; and these costs were summarised in a review by Grosse (2015) and the HTA (Snowsill et al 2014). Adherence data were obtained from two studies conducted in South Africa (Bruwer et al 2013; Bruwer et al 2013). Information on economic and cost analysis methodology were derived predominantly from Drummond et al (2005) and Gray et al (2012) and published studies on cost analysis of health programmes (Subramanian et al 2010; Sinanovic et al 2006; Sinanovic et al 2003). Around 14 studies conducted on Lynch Syndrome in South Africa were retrieved. However, these studies involved the clinical aspects of the disease (Stupart et al 2009; Wentwink et al 2010; Hitchins et al 2011; Hameed et al 2005); quality of a mobile colonoscopy service (Anderson et al 2005) and adherence and uptake rates (Bruwer et al 2013; Bruwer et al 2013). No local study involved the economic aspects related to providing a colonoscopy screening service for Lynch Syndrome individuals. Grey literature such as policy documents (National Department of Health: Sub-directorate Human Genetics, 2000), standard operating procedures for genetic testing (Division of Human Genetics, 2015) and colonoscopy (GSH Gastroenterology Department, 2011), as well as draft protocol documents (GSH Gastroenterology Department, 2015) were

reviewed. Protocols on guidelines for the genetic testing procedures were not finalised at the time of the study. Thus, actual procedures, based on the draft protocols and observation at the time of the study, were assessed.

2. Update on Lynch Syndrome

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) defined LS as an autosomal dominant disorder that predisposes individuals to certain cancers, with colorectal cancer as a major clinical consequence (Palomaki et al. 2009). Individuals with LS may or may not have cancer. EGAPP recommended that the previously used term, hereditary nonpolyposis colorectal cancer (HNPCC), be abandoned (Palomaki et al. 2009). LS is due to mutations in the mismatch repair (MMR) genes and persons with this disorder display high rates of multiple primary tumours, have an early age of onset of cancer and generally have an absence of typical risk factors (Vasen et al. 2013).

Aldried Warthin first described Lynch Syndrome as far back as 1913 (Giardiello et al. 2014; Wolf et al. 2013; Lynch et al. 2015). In 1966, Dr Henry T Lynch provided further insight when he described families with this hereditary colorectal predisposition. He found that 60% to 80% of these colorectal tumours were located in the proximal colon compared to about 30% in sporadic cancer High rates of synchronous and metachronous colorectal cancer with a Chrons-like pattern were also observed. Other LS-associated include endometrial cancer, cancers of the small bowel, stomach, hepatobiliary tract, pancrease, ureter, ovaries, renal pelvis, breast, prostate, sebaceous glands and glioblastoma, amongst others (Giardiello et al. 2014; Lynch et al. 2015). Diagnosis of LS has progressed over the past two decades to include differential diagnosing (family history, clinical phenotype, histopathological characteristics) and definitive diagnosing (germline testing). Since 2000,

over a period of 12 years, commercial genetic testing became available for the four MMR genes plus *EPCAM*. With the recent introduction of next-generation sequencing panels, additional genes are likely to be associated with LS (Giardiello et al. 2014; Wolf et al. 2013; Lynch et al. 2015).

3. Aetiology

The underlying deoxyribonucleic acid (DNA) mismatch repair (MMR) gene defect was discovered in the early 1990's (Palomaki et al. 2009; Giardiello et al. 2014; Wolf et al. 2013). Mutations were found in one of the MMR genes; namely, *MLH1, MSH2, MSH6* or *PSM2*. Up to 90% of mutations in LS are found in *MLH1* and *MSH2*, and around 10% of mutations in *MSH6.* More recently, deletions of the 3' end of *EPCAM* (directly upstream of the *MSH2* gene) were reported and these deletions resulted in epigenetic hypermethylation of the *MSH2* promoter, thereby resulting in Lynch Syndrome. MMR genes produce MMR proteins involved in detecting and correcting DNA replication errors. A defect in the MMR system leads to loss of function of the entire MMR complex and an inability to restore base-base mismatches and small insertions and deletions in DNA sequences. This results in an accelerated accumulation of genetic mutations which often progresses to carcinogenesis. Although mutations occur all over the genome, repetitive DNA sequences such as microsatellites are particularly prone to these mutations. This phenomenon of abnormal patterns of microsatellite repeats is referred to as microsatellite instability (MSI). MSI occurs in more than 90% colorectal cancers in LS and together with age of onset of disease and familial findings, MSI is a strong predictor of LS (Palomaki et al. 2009; Giardiello et al. 2014; Wolf et al. 2013).

Thus far, 19 different mutations in the MMR genes have been identified (as at Nov 2015) in the 62 families on the DNA database (HREC: REF: 217/2010) that formed part of our study. Of these, five common founder mutations have been associated with our cohort. The commonest mutation found in about 30% of these individuals was *MLH1C12528T*.

4. Prevalence and risk

Globally, colorectal cancer is noted as the third most common cancer and cause of cancer-related deaths. It is estimated that the global annual incidence of colorectal cancer is more than 1 million (Graham et al 2012; Wentwink et al 2010). In 2008, colorectal cancer accounted for more than 600 000 deaths, of which 70% occurred in low and middle income countries. The most common cause of hereditary colorectal cancer is Lynch Syndrome which accounts for approx. 3% to 5% of all colorectal cancers (Graham et al. 2012; Vasen et al. 2013; Snowsill eta al. 2014).

In South Africa, colorectal cancer is the fifth most common cancer, with approximately 4 697 new cases and 3 138 deaths reported in 2012 (National Health Laboratory Services: Globocan, 2015). Just over half of the new cases diagnosed and 41% of deaths occurred in individuals younger than 65 years of age (National Health Laboratory Services: Globocan, 2015). Though adequate recording of colorectal cancer incidence exists in South Africa, estimates for LS are lacking as a formal reporting system for Lynch Syndrome does not exist (Coetzee et al. 2013). Other than the LS register (DNA database HREC: REF: 217/2010) maintained by the University of Cape Town (UCT), there are very few, if any hereditary colorectal cancer registries in South Africa (Coetzee et al. 2013). With information from this register, Vergouwe, et al (2013) showed that inherited cancers

formed a three times bigger proportion of the total burden of colorectal cancer in a low-prevalence area for colorectal cancer compared to high prevalence areas i.e. 10,5% vs 3%. He postulated that in low incidence areas such as South Africa, the prevalence of inherited cancers may be higher than the established values in the literature (Vergouwe et al, 2013).

The risks of developing cancers associated with LS are continuing to evolve with the increased application of germline testing and these risks are highly MMR gene mutation and sex dependent (Bonadona et al. 2011; Giardiello et al 2014). A person with LS has a 25% to 75% risk of colorectal cancer i.e. up to 1 in 3 people will develop colorectal cancer before the age of 70 years if there is no intervention. Though more recent studies have presented lower lifetime risks of 50%, this is still ten times higher than risks in the general population. Evidence suggests that *MLH1* and *MSH2* are the most widely distributed and has the highest risk of cancer. An evidence review performed by EGAPP (2009) reported that there is limited data that implies distributions of mutations of 32% in *MLH1*, 38% in *MSH2*, 14% in *MSH6* and 15% in *PMS2*. Snowsill et al. (2014) reported distributions of mutations based on 12 624 observations internationally; i.e. 39% in *MHL1*, 34% in *MSH2*, 20% in *MSH6* and 8% in *PMS2*. This information, however, is context specific and bias in terms of local referral guidelines. In the UCT cohort that will be used in this study, *MHL1* and *MSH2* mutations were identified, but to date no *MSH6*, *PMS2* and *EPGAM* mutations have been identified (Voster, A: Division of Human Genetics: UCT, personal communication 2015). The highest risks, in the region of 40% to 70%, were associated with individuals with *MLH1* and *MSH2* mutations (Bonadona et al. 2011; Giardiello et al. 2014). Lower risks were reported for *MSH6* (10% - 22%) and *PMS2* (15% - 20%). For men the risk of colorectal cancer was reported to be higher than for women i.e. 38% - 45% compared 31% - 35% (Bonadona et al. 2011; Giardiello et al. 2014). The MMR mutation distributions for the UCT DNA database cohort indicated a population that falls in the

highest risk category (predominantly *MLH1* & *MSH2*), reinforcing the need for an effective screening programme. Currently, due to resource constraints, the Division of Human Genetics: UCT appropriately directed their genetic testing strategy predominantly on the common founder mutations in the *MLH1* and *MSH2* genes.

In LS, the mean age at diagnosis of colorectal cancer is 41 to 66 years, whereas for the general population diagnosis is usually at around 69 years (Giardiello et al 2014; Bonadona et al. 2011; Cohen et al. 2014; Snowsill et al. 2014)). Furthermore, about half of colorectal cancer cases develop before the age of 50 years in LS compared to 10% in the general population. The estimated cumulative risks in carriers began to increase from the age 30 years irrespective of the gene mutation involved. Also, approximately 15% - 20% of cancer survivors with Lynch Syndrome will develop a second colorectal cancer within 10 years, 40% - 50% within 20 years and >60% within 30 years. Progression of adenoma to carcinoma is accelerated in individuals with Lynch Syndrome compared to sporadic and familial colorectal cancers. In Lynch Syndrome polyps may progress to carcinoma within 2 to 3 years as opposed to 8 to >10 years in the general population (Giardiello et al 2014; Bonadona et al. 2011; Cohen et al. 2014; Snowsill et al 2014). It is clear from the evidence that individuals affected by this disorder are in the age range of persons that are usually economically active and support families and, thus, the impact of this disorder stretches wider than just the individual. Delaying or preventing the onset of cancer would, therefore, be desirable. Furthermore, due to the autosomal dominant nature of the disorder, if one parent has an MMR mutation, this mutation will be inherited by his or her child i.e. the first degree relative (FDR) has a 50% chance of having LS (Snowsill et al. 2014). A first degree relative is a parent, child or sibling. EGAPP noted that there is limited, but promising evidence that testing / screening a patient for LS will impact on clinical management that will significantly improve health-related outcomes (Palomaki et al.

2009). Risk-reducing strategies may be offered such as early treatment of cancer, surgical interventions and cascade testing of relatives (Palomaki et al. 2009).

5. Diagnosing Lynch Syndrome

Diagnosing individuals with LS is key in the management of this disorder as these individuals can benefit from life-saving intensive cancer screening (Giardiello et al 2014; Vasen et al 2013; Lynch et al 2015). It is believed that LS is underdiagnosed due to the intricacy of diagnostic strategies, and thus, poor implementation of these strategies (Vasen et al. 2013). Accessibility and lack of awareness amongst the general population further contributed to the underdiagnosing of LS (Vasen et al. 2013).

Technology for identifying LS is rapidly advancing, making it problematic to compare earlier studies and recent studies (Snowsill et al. 2014). Furthermore, heterogeneity amongst the studies and robustness of testing methods make pooling of data difficult. A number of strategies exist for diagnosing LS (Giardielloe et al 2014; Lynch et al 2015; Snowsill et al 2014; Vasen et al 2013). Differential diagnosis includes family history, histopathology and prediction models. Definitive diagnosis involves identification of the MMR mutation by genetic testing (Lynch et al. 2015). Low specificity of tests would result in a high number of false positives and individuals may be informed that they have LS when they do not; and as a consequence be exposed to invasive and potentially hazardous procedures unnecessarily. Low sensitivity would result in a high number of missed cases (Snowsill et al. 2014).

5.1 Family history and computational models

Family history is still considered an important element in assessing risk in the general population (Palomaki et al. 2009; Giardiello et al. 2014; Vasen et al. 2013). The Amsterdam criteria exhibited a relatively low sensitivity of 22% and a specificity of 98% for diagnosing LS. The Revised Bethesda Criteria (See Table 1), also, did not deliver the necessary sensitivity (82%) and specificity (77%) as a preliminary screening test (Polomaki et al. 2009; Giardiello et al. 2014). Challenges with consistency in collecting information, time taken to collect information and accuracy of information collected contributed to the recommendation by EGAPP to remove family history as a preliminary test for patients newly diagnosed with colorectal cancer (Palomaki et al. 2009).

Table 1: Revised Bethesda Criteria

1. Colorectal cancer diagnosed at younger than 50 years.
2. Presence of synchronous or metachronous colorectal cancer or other LS-associated tumours#.
3. Colorectal with MSI-high pathologic-associated features (Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old.
4. Patient with colorectal cancer and colorectal cancer or LS-associated tumour diagnosed in at least 1 first-degree relative younger than 50 years old.
5. Patient with colorectal cancer and colorectal cancer or LS-associated tumour at any age in two first-degree or second-degree relatives.

#LS-associated tumours include tumour of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and kerotoacanthomas.

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Computational models such as *MMRpredict*, *MMRpro* and *PREMM* are available online and perform better than the Revised Bethesda Criteria (Giardiello et al. 2014).

5.2 Immunohistochemistry

Immunohistochemitry (IHC) testing is a preliminary test performed on tumour tissue and assists in identifying the MMR gene (*MLH1, MSH2, MSH6* or *PSM2*) that is most likely to have a mutation (Giardiello et al. 2014; Snowsill et al. 2014; Hedge et al. 2013). IHC, thus, has the added advantage of directing germline testing to a specific gene. Patients with a negative stain would suggest high risk for LS and the individual may, therefore, be recommended for DNA analysis of the relevant gene. There is a lack of good quality evidence for estimating IHC sensitivity and specificity. The EGAPP reported, based on moderate evidence, sensitivity of approximately 83% irrespective of MMR gene involved, and specificity of 88.8% (with wide variations) (Palomaki et al. 2009; Giardiello et al. 2014; Snowsill et al. 2014; Hedge et al. 2013). The Health Technology Assessment (HTA) conducted by the National Institute for Health Research reported IHC sensitivity that ranged from 73% - 100% and specificity that ranged from 12.5% - 100% (Snowsill et al. 2014). As IHC is performed on tumour tissue, not all patients will be able to undergo IHC.

5.3 Microsatellite Instability

Microsatellite Instability (MSI) testing is a preliminary test performed on the tumour tissue to identify suitable candidates for germline testing (Snowsill et al. 2014). Patients with a high instability would proceed to immunohistochemistry or genetic testing as 10 – 15 % of patients with a high instability have sporadic colorectal cancer. Sensitivity and specificity may vary depending on the number of mononucleic markers included, test methodology and protocol for sample preparation. The HTA conducted by the National Institute for Health Research (2014) reported an MSI sensitivity range from 88% to 100%, but a lower specificity range from 68% to 84% (Snowsill et al. 2014). The EGAPP reported, based on

moderate evidence, sensitivities of approximately 89% (for *MLH1* & *MSH2*) and about 77% for *MSH6* (Palomaki et al. 2009). About 5% of MSI have normal IHC results and therefore, it was suggested that both IHC and MSI be performed or to proceed directly to gene testing (Hampel 2009; Hedge et al. 2013). MSI testing is labour intensive, expensive and requires a skilled geneticist (Coetzee et al. 2013).

5.4 *BRAF V600E*

Most colorectal cancers with *BRAF V600E* mutations are associated with MSI positive results (Giardiello et al. 2014; Snowsill et al. 2014; Hedge et al. 2013). Almost always, an MMR mutation is not present when *BRAF V600E* mutation is found. Performing *BRAF V600E* testing on tumours with absent *MLH1* staining would identify patients that would not benefit from *MLH1* sequencing. Literature suggested that significant cost savings could be implicated as *BRAF V600E* testing is relatively inexpensive compared to *MLH1* sequencing and *MLH1* is the most common MMR gene associated with absent IHC staining. Sensitivity and specificity of *BRAF V600E* testing is estimated as 69% and 100%, respectively, based on moderate evidence (Giardiello et al. 2014; Snowsill et al. 2014; Hedge et al. 2013).

5.5 Genetic testing

Advantages of genetic testing include:

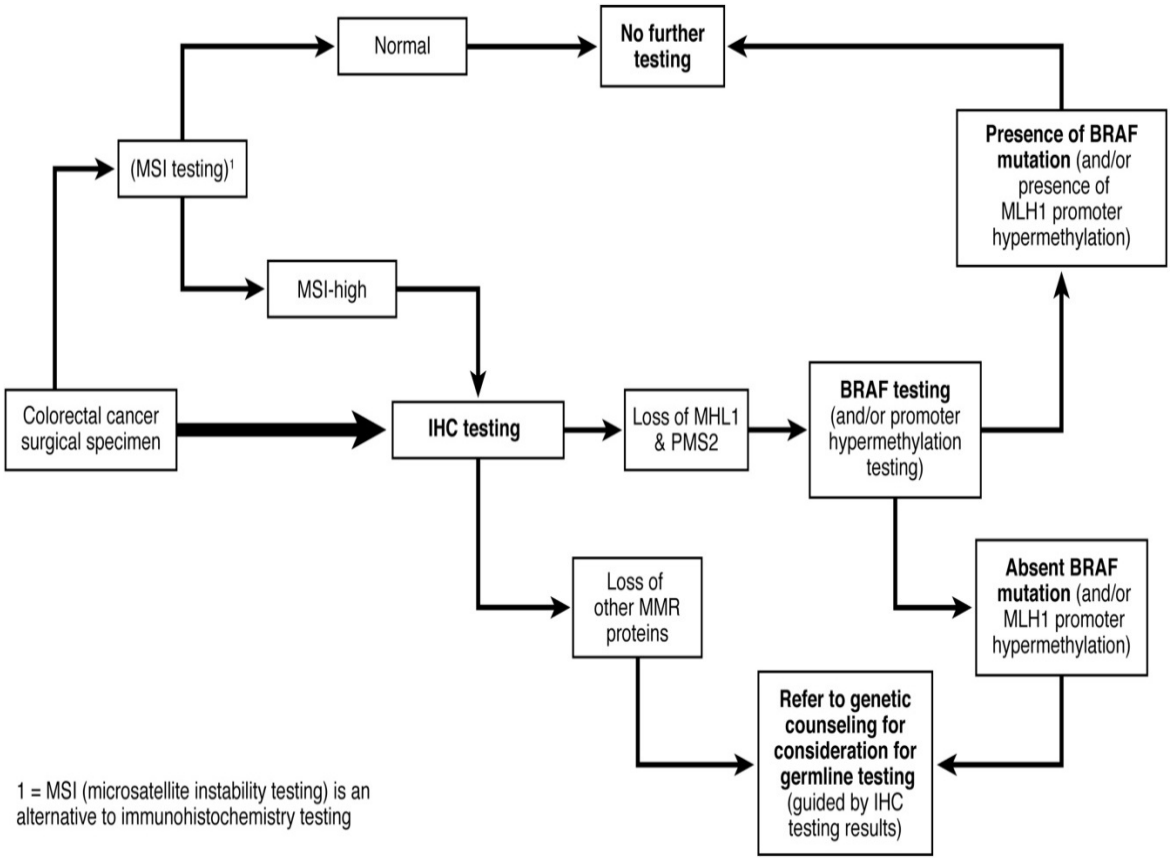
- confirmation of diagnosis in a proband / family,
- confirmation of the diagnosis in an at-risk family member when the mutation is known and,
- appropriate management can be offered for LS diagnosed individuals and those who tested negative for LS (Giardielo et al. 2014).

Genetic testing in LS is complex as (i) there are a number of cancers to consider in the differential diagnosis, (ii) there is considerable overlap in phenotype and (iii) the testing involves a combination of germline tests and tumour tests (Hampel 2009). It is anticipated that Next-Generation Sequencing (NGS) will allow for simplification of this process as it will provide for the sequencing of all genes involved in LS-associated colorectal cancer in a panel; and at possibly a more reduced cost. (Hedge et al. 2013). Testing strategies are illustrated in Figs 1, 2, 3 and 4 (Giardiello et al. 2014). Studies have shown that up to 25% of LS patients would be missed with the most generous clinical criteria and thus, EGAPP proposed universal testing for persons with colorectal cancer. Although this strategy was supported by the National Comprehensive Cancer Network and other groups, implementation is challenging, especially in resource constrained environments. In these circumstances, traditional testing has been a preferred option (Giardiello et al. 2009).

5.5.1 Universal testing

Universal testing (Fig 1), as proposed by EGAPP, involves testing of all persons with colorectal cancer ≤70 years, and >70 years with a family history suggesting risk for LS (GRADE moderate quality evidence) (Giardiello et al. 2014).

Fig. 1: Universal screening



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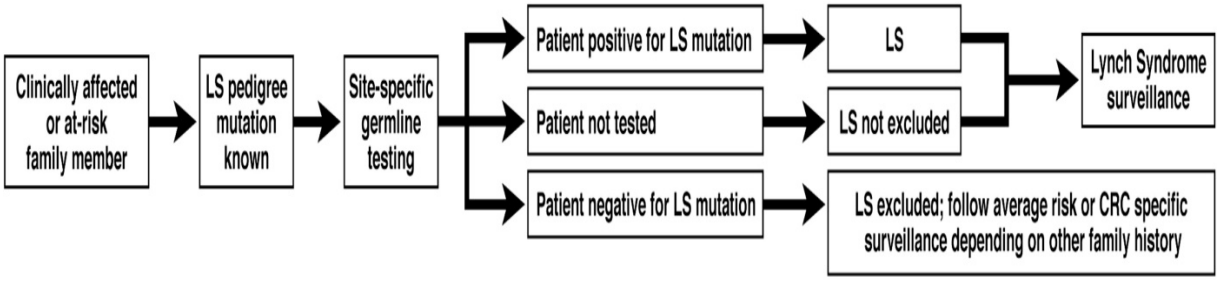
5.5.2 Traditional testing

Traditional testing involves selective genetic testing based on:

- tumour displaying MMR deficiency; or
- Revised Bethesda Criteria; or
- Amsterdam Criteria; or
- Uterine / endometrial cancer at <50 years; or
- known mutation in family;
- or / and personal risk ≥25% on prediction models.

If the mutation is known (Fig. 2), a negative genetic test result for the mutation on the pedigree would indicate that the pedigree does not have LS (GRADE moderate quality evidence) (Giardiello et al. 2014).

Fig. 2: Traditional testing strategy in the case of a known family mutation



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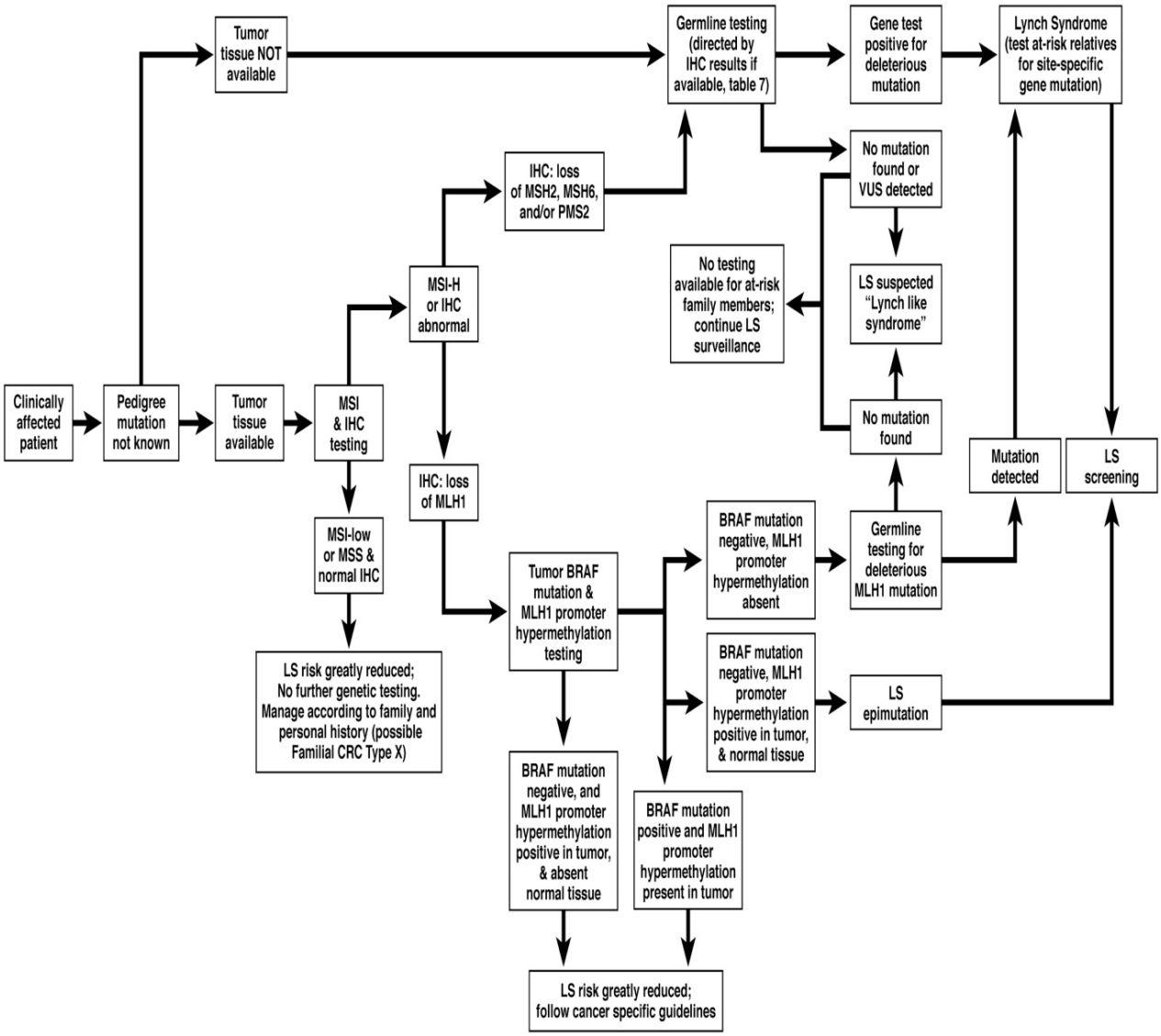
In the case of an affected person (i.e. has cancer) where the mutation is unknown (Fig. 3), IHC and / or MSI would be recommended. If these results do not suggest an MMR mutation, LS is excluded and no further testing is recommended. Conversely, if results are positive, genetic testing would be recommended (Giardiello et al. 2014).

Fig. 3: Traditional testing strategy in the case where the patient is clinically affected and mutation in the family is unknown



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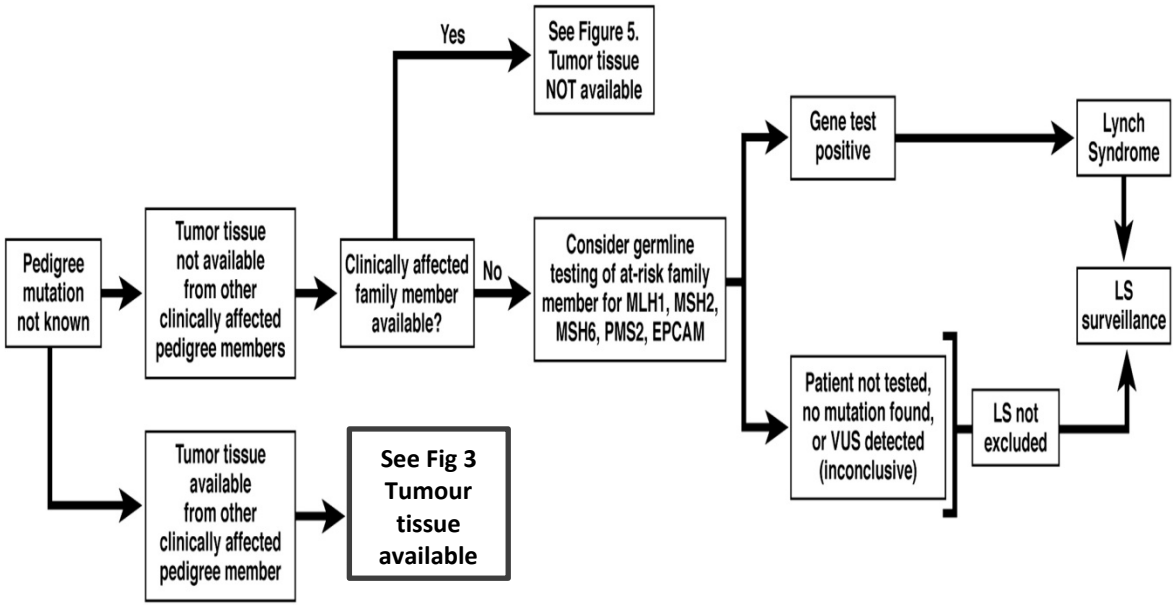
In the case of an at-risk person (person with no cancer) where the family mutation is known, the at-risk person and relevant family members can be diagnosed for LS by genetic testing. Where the family mutation for the at-risk patient is unknown, it is suggested that an affected member be found and, if possible, evaluation of the tumour is suggested, which will direct genetic testing. If an affected member is not found, genetic testing can be performed as per Fig. 4.

Fig. 4: Traditional testing strategy in the case of an at-risk patient (do not have cancer yet) and an unknown family mutation



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Guidelines further recommended that genetic testing should not be offered to at-risk relatives until the mutation had been identified (Vasen et al. 2013; Giardiello et al. 2014). At-risk relatives can then undergo single mutation testing (predictive testing) for the identified gene which is less expensive and reliable. Relatives that have the mutation(s) and defer genetic testing should be treated the same as patients with Lynch Syndrome, whereas relatives that tested negative would follow screening frequency as per the general population. Literature suggested that for every proband, an average of 3 relatives could be tested for LS at a much lesser cost than the cost of testing a proband – thus, reflecting the benefit of identifying a proband (Vasen et al. 2013). Positivity rates of relatives of 39% to 50% were reported for studies conducted in high income countries (Grosse et al. 2015). This means that for every two relatives tested, up to one may test positive.

5.5.3 Genetic testing procedures

Various strategies have been applied to perform genetic testing for LS and to date there are no clear guidelines on best practice (Hampel 2010; Snowsill et al 2014). Practices can become fairly complex and may involve some or all of the following preliminary tests; IHC, MSI, or *BRAF V600E*. Genetic testing involves DNA extraction, polymerase chain reaction (PCR), restriction enzyme digest, Multiplex Ligation-dependent Probe Amplification (MLPA) and / or Sanger sequencing (Hampel 2010).

- PCR amplifies the fragment of DNA carrying the site of the mutation (Hedge et al. 2014);
- Restriction enzyme digest specifically recognize the mutated DNA sequence and cut it. The cut (mutation positive) and uncut (mutation negative) fragments are distinguishable on an agarose gel run in an electric field.
- Sanger sequencing produces a graphic read out showing the exact site of the mutation.
- Multiplex Ligation-dependent Probe Amplification (MLPA) detects deletions/insertions of whole exons of the respective gene(s) (Hedge et al. 2014).

Snowsill et al (2014) reviewed the performance of genetic tests and resolved that Sequencing with MLPA was recognised as the gold standard for diagnosing LS.

Standard operating procedures for genetic testing (Division of Human Genetics, 2015) informed on the actual procedures followed to perform the specific genetic tests for this study. However, the guidelines in terms of which tests to perform was not finalised (GSH Gastroenterology Department and UCT Division of Human Genetics, in progress). Therefore, actual procedures, based on the draft protocols and observation at the time of the study, was recorded for this study.

6. Genetic counselling & patient support

Genetic counselling, by a trained health professional, includes pre-test, post-test and follow-up counselling with every colonoscopy screening session (Giardiello et al 2014). Appropriate standards and certifications are required as genetic counsellors have to be competent in order to deal with psychological, clinical, ethical and financial issues. Counselling involves informing patients, obtaining informed consent, constructing pedigree trees and disclosure of test results (Giardiello et al 2014). The most cost-effective approach, under limited funding, is to improve diagnosis in relatives of persons that have already been screened (Vasen et al 2013; Grosse 2015). Genetic counsellors play a key role in recruiting relatives for testing. Uptake rate of genetic testing in a local study were reported as reasonably high i.e. 97% and 74% for siblings and children, respectively (Bruwer et al. 2012).

7. Screening for colorectal cancer

Colorectal cancer is generally asymptomatic before the cancer has reached a relatively advanced stage (Vasen et al. 2013). The majority of colorectal cancers develop from a polyp, a premalignant form that may exist for years before symptoms of cancer manifest (Lynch et al. 2015). Individuals with LS can benefit from life-saving intensive screening and thus, it is crucial that these individuals be identified via an effective screening programme (Vasen et al. 2013).

Faecal occult blood tests (FOBTs) detect mainly asymptomatic cancers by detecting blood from bleeding cancers (Coetzee et al 2013). Sensitivity of a single FOBT is about 30% as cancers only bleed intermittently. Although cheap and non-invasive, the low sensitivity of

FOBT is not ideal for screening for LS. Flexible sigmoidoscopy is less technically demanding and less invasive than colonoscopy and does not require full bowel preparation. This procedure allows for visualisation, removal of polyps and tissue biopsy of the left colon. However, about two thirds of Lynch Syndrome-associated colorectal cancers appear proximal to the left colon and may be missed (Lynch 2015; Coetzee et al 2013).

Colonoscopy allows for inspection of the entire colon and, if performed by a skilled professional, provides a sensitivity of up to 100% for detecting cancers and advanced adenomas (Coetzee et al 2013). Two main advantages of appropriate screening are the early detection of cancer and consequently enhances prospects of curative treatment and secondly, the early detection of pre-cancerous lesions which allows for removal of the polyps before it can advance to cancer. There are no randomised controlled studies on routine colonoscopy screening. However, Level IIb evidence (well-designed quasi experimental study) exists that indicated a reduced incidence of colorectal cancer by 62% and 65% - 70% decrease in mortality (Jarvinen et al. 2009; Vasen et al. 2013). In a South African cohort from the same community as this study, Stupart et al (2008) showed that 27% of patients in a no-colonoscopy screening group developed colorectal cancer as opposed to 11% in the group that received colonoscopy screening. In the same study, death from colorectal cancer occurred in 12% of the group that did not undergo colonoscopy screening compared to only 2% in the colonoscopy screening group (Stupart et al. 2008).

Colonoscopy is more invasive, requires sedation and bowel preparation, and has morbidity associated with this procedure (Coetzee et al 2013; Snowsill et al 2014). The most common, serious adverse events related to colonoscopy in the general population are death 0.08/1000, perforation (3.3/1000) and bleeding (11.1/1000) (Palomaki et al 2009). Compliance with colonoscopy is, therefore, lower compared with other procedures.

Adherence to colonoscopy ranged from 60% to 88% in studies conducted in high income countries (Gross 2015). Stupart et al (2008) reported an uptake of 72% in the South African cohort. A very low adherence rate to colonoscopy of 25% was reported in another South African study conducted on LS-positive persons over a 5-year period (Bruwer et al. 2013). Uptake of colonoscopy depends on access to services, acceptance of services, awareness and availability of resources.

Relatives without the mutation(s) should follow cancer screening guidelines as for the general population i.e. every ten years from the age of 50 years. (Giardiello et al. 2014; Snowsill et al. 2014). For LS individuals, most guidelines recommend that biennial colonoscopy should commence at the age of 20 - 25 years or two to five years before the age of the youngest person diagnosed with colorectal cancer in the family. Furthermore, biennial colonoscopy is recommended up to 29 years and annual colonoscopy for persons from 30 to about 60 years or when the risks of colonoscopy outweigh its benefit. It has also been recommended that, due to the reduced penetrance, individuals with *MSH6* or *PMS2* may commence colonoscopy screening as late as 30 years and 35 years, respectively (Giardiello et al. 2014; Snowsill et al. 2014).

Public sector colonoscopy services in South Africa cater for approximately 80% of the country's population and are few and limited to secondary and tertiary level care. Furthermore, these colonoscopies are only performed by medical or surgical gastroenterologists. Although there is evidence that simple endoscopy procedures could be provided by non-physicians safely and effectively, there is a paucity of data on non-physicians providing colonoscopy (Day et al. 2014; Ruco et al. 2016). Due to the limited professional skills and services available, colonoscopies are generally not for screening purposes, but are performed on patients that present with symptoms in order to exclude cancer (Personal communication: Thomson, S: Gastroenterology clinic: GSH. 2015).

8. Cost analysis

Genetic-based interventions are complex interventions that can guide clinical decision-making in terms of accurate diagnosis, more focused treatment, potentially limit or prevent disease, prevent hazardous or unnecessary treatments, prolong life and overall promote health (Grosse et al 2008; Buchanan et al 2013). Furthermore, genetic information can guide patients and family members in terms of decision-making regarding their own health. In most cases, genetic testing provides information for decision-making, but may not have any direct impact on mortality or morbidity. Screening, similarly, provides information for further action (e.g. polypectomy, curative treatments, etc.). For both genetic testing and colonoscopy, benefits are received later in time. Both these technologies will impact significantly on the consumption of resources. It is imperative, therefore, for decision-makers to assess the benefits and costs of genetic and screening technology; and be able to compare these benefits and costs to various other options (Grosse et al. 2008; Buchanan et al. 2013). Economic evaluations are systematic analysis of relevant healthcare alternatives in order to compare both costs and consequences of alternative options with the intention of informing on a preferred course of action (Drummond et al. 2005). Economic evaluations commonly encountered in healthcare include cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). A CEA compares cost and consequences (effectiveness) of different alternatives and generally, only one outcome is considered per cost incurred. Outcomes for CEA are measured in natural units (e.g. blood pressure – mmHg). A CUA compares costs and consequences in terms of patient utility (e.g. quality adjusted life year – QUALY) and more than one outcome may be considered for the patient (Drummond et al. 2005). The limitation of performing a CUA for genetic testing is that, generally, QUALYs (utilities) are calculated directly for the affected individual. The extended effect (benefit or harm) to

family members in terms of knowledge for informed decision-making are often excluded and would require specific modelling in order to be considered. Cost-benefit analysis (CBA) considers costs and a broad range of different patient outcomes. In a CBA both costs and outcomes are valued in monetary terms (Drummond et al. 2005). CBAs take into consideration both health and non-health outcomes, and my not be useful if a decision-maker only wants to focus on optimising health outcomes (Grosse et al. 2008).

Partial economic analysis allow for important intermediate stages of understanding the costs and consequences of alternative healthcare programmes (Drummond et al. 2005; Gray et al. 2012). In this study, a partial economic evaluation will be performed that focuses on costs i.e. collecting primary data to determine the cost of providing colonoscopy and germline tests for patients with Lynch Syndrome and their relatives. The reason for collecting primary cost data is that even with attempts to standardise costing methodologies, availability of financial data and financial practices impact on results and therefore, data is very much time, context and country specific. Furthermore, estimating costs from medical charges may not produce accurate results as charges may be influenced by factors such as service provider monopolies, cross-subsidisations, profit generation or negotiated contracts (Drummond et al 2005; Gray et al. 2012).

Table 2 reflects the costs reported in various cost-effectiveness studies performed in different countries (Gross 2015). Total screening costs were around $2 242 to $3 345. One study was unusually high at a total cost of $6 312. Generally, the largest contributors towards the screening costs were the genetic testing for MLH1 and colonoscopy. Long-term the colonoscopy cost will be the main cost driver as the other costs are once-off costs. The lowest cost contributors were the genetic counselling costs and approaching relatives. The predictive tests for relatives were in all cases significantly lower than the genetic sequencing for MLH1 (identifying the mutation). This indicates the value of identifying a

family mutation – i.e. relatives may be identified at a much lower cost and may benefit more from colonoscopy screening as they may not have cancer yet as opposed to the proband who often present with cancer already.

Table 2: Base case estimates of costs of routine testing and colonoscopy for Lynch Syndrome in patients with colorectal cancer and first degree relatives, in 2014 US $

Study	Pre-test counselling	Post-test counselling	Counselling for gene sequencing	IHC	Gene sequencing for *MLH1* gene	Approaching relatives	Test for relative (predictive)*	Combined test and counselling cost for relatives	Colonoscopy unit cost	TOTAL COST
Mvundura et al. (2010) USA	22	106	194	290	899	350	61	441	1043	3345
% of total cost	0.66	3.17	5.80	8.67	26.88	10.46	1.82	13.18	31.18	100
Ladabaum et al (2011) USA	NR	112	198	300	942	118	492	610	690	2970
% of total cost	NR	3.77	6.67	10.10	31.72	3.97	16.57	20.54	23.23	100
Sie et al (2007) Netherlands	25	136	0	184	1184	77	353	430	206	2242
% of total cost	1.12	6.07	0	8.21	52.81	3.43	15.74	19.18	9.19	100
Snowsill et al (2014; 2015) UK	0	0	103	366	714	103	265	368	911	2565
% of total cost	0	0	4.02	14.27	27.84	4.02	10.33	14.35	35.52	100
Severin et al (2014) Germany	57	161	0	166	5268#	57	281	338	265	6312
% of total cost	0.90	2.55	0	2.63	83.46	0.90	4.45	5.35	4.20	100
Barzi et al (2015) USA	NR	112	198	300	942	118	492	610	690	2970
% of total cost	NR	3.77	6.67	10.10	31.72	3.97	16.57	20.54	23.23	100

NR: Not reported * Not added to total (included in combined counselling and test)

Genetic testing costs is not higher in Germany. The German reimbursement for gene sequencing is an outlier.

Adapted from Grosse 2015. *Healthcare.* 3, 860-878.

The perspective and target audience assumed in an economic analysis are significant as these inform on the costs and other considerations that will be included in the analysis (Drummond et al. 2005; Grosse et al. 2008). Most economic analyses are performed from the provider perspective; however a more societal approach may be more appropriate for genomics due to its indirect impacts (Buchanan et al 2013). Furthermore, health practitioners place significant value on informed decision-making by the patient, whereas

for health care payers this may not be relevant (Buchanan et al 2013). For this study, however, a health provider perspective will be applied as the aim of the study is to estimate and compare the cost of colonoscopy screening as a step towards assessing affordability. In this case, the key target audiences will be the service providers, policy makers, government and researches.

Costs may be determined by stochastic analysis i.e. understanding that the resources required may vary from patient to patient due to known and unknown variables, and therefore cannot be predicted accurately (Gray et al. 2012). In this case, in practice, the variations between patients may be considerable. In a deterministic analysis, a model treatment is assumed per patient and costed. (Gray et al. 2012). Germline testing for identifying the responsible MMR gene mutation may have significant variation in cost between patients as the number of tests required to identify the gene mutation vary from patient to patient (Buchanan et al. 2013). In many cases, genetic testing has a research arm associated with it which impacts on testing procedures applied. For LS, national standard protocols for genetic testing are not established and practices may vary from laboratory to laboratory. The timing of collecting costs is also important as standard practices for genomic interventions evolves over time and different techniques have different sensitivities and specificities (Buchanan et al. 2013). To overcome these challenges, and as recommended by Grosse et al. (2008) costs should, therefore, be based on actual utilization data and processes followed at GSH and UCT. Additionally, analysis of data should be restricted to a specific period to ensure that the latest technologies used at GSH / UCT were considered only.

Three stages are generally involved in performing a cost analysis i.e. (i) identifying resources required, (ii) measuring / quantifying these resources using physical units and

(iii) valuing these resources (Drummond et al. 2005; Gray et al. 2012; Mangham 2009). Two approaches are commonly used for identifying resources; namely, gross-costing (referred to as top-down costing) and micro-costing (referred to as bottom-up costing) (Drummond et al. 2005; Gray et al. 2012). Gross-costing identifies costs in bundles e.g. cost of a day in hospital, whereas micro-costing involves identifying and costing all activities, consumables, staff, etc. related to the day in hospital. The approach used will depend on the ease of collecting the data and the resources-use difference between the comparisons (Gray et al. 2012). Since very little costing data and bundle costs estimates are available on colonoscopy and germline testing in the public sector, a predominantly micro-costing approach is more appropriate. Measurement of resource quantities may be collected by observation, patient or staff interviews, completing questionnaires or folder reviews. Valuing of resources should, ideally, reflect opportunity costs. In practice, market prices are assumed to be a reasonable approximation of opportunity costs (Drummond et al. 2005; Gray et al. 2012). Market prices, however, have an element of profit attached to it ((Drummond et al. 2005; Gray et al. 2012) and in the public sector in South Africa, prices may differ significantly between private and public sector. In South Africa, the Uniform Patient Fees Schedule (UPFS) is used as a reference price list in the public sector to reflect State prices (Department of Health: Western Cape 2015). These prices for services are often approximations and not always based on actual costs (Personal communication: Kathrie-Salie, M: Directorate Finance: Department of Health - Western Cape). Thus, in our study, resources for services will be valued by collecting primary data rather than using reference lists, hospital charges or market prices.

Costs are estimated in terms of capital costs and recurrent costs (Drummond et al. 2005; Gray et al. 2012). Capital costs are investments made at a single point in time and represent an investment in assets used over a period of time. The cost of a capital item is

associated with the lost opportunity of investing the capital expenditure for an alternative benefit. Most capital costs depreciate over time, while some, such as land and buildings maintains its value and are non-depreciable. The "equivalent annual cost" is determined by annuitizing the initial capital expenditure. Annuitizing takes into account opportunity cost, depreciation and the life-years of the capital item. Recommended discounting rates for annuitizing is 3%. Life-years of a capital item or equipment reflect the number of usable years of the item (Drummond et al. 2005; Gray et al. 2012). – Buildings are usually allocated usable life-years of 30 to 50 years, equipment five to ten years, and furniture one to five years (Drummond et al. 2005; Gray et al. 2012; Mangham 2009; Somda 2007).

Shared costs (e.g. overhead costs) may be allocated in a variety of ways, but are usually allocated based on the different activities that drive the departments e.g. paid hours for staff, square metres for housekeeping, etc. (Drummond et al. 2005; Gray et al. 2012). The unit used to determine the allocation of shared costs must be as homogenous as possible with regards to cost across services and must be associated with every patient concerned (Drummond et al. 2005; Gray et al. 2012).

Total costs provide policy makers and service providers with information of total expenditure, budget requirements and affordability (Drummond et al. 2005; Gray et al. 2012). Average unit cost data provide information, on average, of cost changes when data is generalised across different settings or patient utilisation patterns. Average unit cost may differ as it may include settings of different levels of production efficiency. Marginal costs provide information on the additional cost for every additional unit produced. This is important for scaling up of services (Drummond et al. 2005; Gray et al. 2012). In our study, average unit costs for colonoscopy and genetic testing will be estimated and this

will be used to calculate total costs based on patient utilisation and expected utilisation patterns.

Programmes with differential timing of resource outlays need to accommodate for time preferences. Most people desire a positive time preference because of (i) opportunity costs, (ii) the value of an amount of money today is worth more than the value of the same amount of money in the future, and (iii) uncertainty of the future. The discount rate is based on a value judgement by society and reflects the extent to which society is willing to postpone their gratification for the benefit of the future generations. Future costs are, thus, discounted to present value. There is not yet consensus on the discount rate to use in economic evaluations. However, discount rates are published in many countries. Discount rates commonly reflected in literature is usually used in countries where discount rates are not published. As the discount rate is a subjective variable, sensitivity analysis on no discount rate and commonly published discount rates such as 3% or 5% are recommended. (Drummond et al, 2005; Department of Health: Government Gazette No. 36118).

Sensitivity analysis is a method that is used to deal with uncertainty (Drummond et al. 2005). Sensitivity analyses are based on uncertainties (parameters) reflected in literature or in our study; and inform on the extent to which these parameters will influence costs or outcomes (Drummond et al. 2005). According to literature, discount rates, adherence to colonoscopy and positivity rate of relatives are main parameters that influence colorectal screening costs in LS (Gross 2015).

9. Cost-effectiveness of screening strategies for Lynch Syndrome

A number of cost-effectiveness studies on LS screening has been published (Snowsill et al 2014; Grosse 2015). However, these studies focused on high income countries and generalisability to the South African context poses a challenge.

A Health Technology Assessment (HTA) published in 2014 included a systematic review of 32 cost-effectiveness studies (Snowsill et al. 2014). Most of the studies were conducted in the United States of America and were designed from a health service provider perspective. The most frequently used test strategy could not be determined from the review as the studies employed different tests and combinations of tests. Furthermore, different studies made different assumptions and this complicated direct comparability of studies. The management strategies across the studies were fairly consistent and included biennial to annual colonoscopy screening from the age of 25 years, with extensive colorectal surgery on diagnosis of colorectal cancer. Many of the studies failed to comply with the Drummond checklist (Drummond et al. 2005). The review could not inform on the consistency with regards to the strategies or individual test that would be most cost-effective. All studies, however, concluded that screening for LS compared to no screening was cost-effective (Snowsill et al. 2014). Similar findings were found in a review by Grosse (2015) who also concluded that cost-effectiveness is subject to the alternative strategies available and the methods of collecting and valuing costs. He further suggested that in order to inform appropriately on cost-effectiveness for screening for LS, unlike most of these studies where a number of assumptions are applied, actual real-life clinical practice should be documented as costs, adherence to colonoscopy, number of relatives tested vary across populations (Gross 2008).

Snowsill et al. (2014) further conducted a health technology assessment comparing eight screening strategies. The more tests that were performed in sequence, the greater the costs as well as the specificity. Little, however, is reported in the literature regarding sensitivity and specificity when performing tests sequentially except for *BRAF V600E* test after IHC or MSI with *MLH1*. The HTA found that, compared to no testing as the base case, MSI + *BRAF* V600E + genetic testing produced the lowest ICER. Sensitivity analysis indicated that, even at low rates of acceptance of diagnostic tests and genetic counselling, LS testing was found to be cost-effective compared to no testing. Sensitivity analysis performed on widely varying the number of relatives per proband, including no relatives, found screening for LS more cost-effective than no screening. LS diagnosis and true LS status greatly influenced life expectancy. The total number of colonoscopies was influenced by the correct diagnosis of LS and adherence to screening. Strategies that increase the number of false positives and reduce the number of false negatives resulted in an increased number of colonoscopies and therefore increased costs. Strategies that identified more LS positive patients reduced the expected number of colorectal cancers for probands and relatives. This is due to the impact of colonoscopy screening as a preventative measure for colorectal cancer. Universal gene testing, therefore, resulted in the lowest number of colorectal cancer in both probands and relatives, but was the most expensive. Clinical outcomes were also strongly influenced by compliance with preventative measures. Higher number of colonoscopies produced less colorectal cancer and higher life expectancies. The majority of the diagnosing cost for the cohort was due to diagnosing the probands, as opposed to diagnosing the relatives. Costs were driven by the number of tests taken. Compared to long-term costs, diagnostic costs were small and did not influence the variation in costs between strategies. The most influential cost driver, long-term, was the cost of colonoscopies. During univariate sensitivity analysis, ICERS were nearly doubled or

halved when colonoscopy costs were doubled or halved, respectively. As QUALY's increased, the total costs increased across the strategies as expected due to the preventative measures used. The time of diagnosis, the age at diagnosis, the stage at diagnosis and the site of the cancer, impacts on the management of colorectal cancer and this may vary substantially from patient to patient. It is, thus, an enormous task to estimate the cost of treating cancer and data cannot be easily generalised. However, in the HTA conducted in the United Kingdom, it was found that preventative costs outweighed the increased savings in cost from colorectal cancer treatment (Snowsill etl al. 2014).

In summary, the number of colonoscopies was the main cost driver; and this was influenced by number of LS positive probands, adherence rate to colonoscopy and number of positive relatives that tested positive.

10. Summary of literature review

- Individuals with LS have a high risk for colorectal cancer and the onset of cancer occurs at ages when persons are economically active and support families. South African families with LS have been implicated with the MMR genes, *MLH1* and *MSH2*, which presents the highest risks (40% to 70%) for colorectal cancer.
- The literature showed a paucity of randomised control trials on the benefit of colonoscopy in colorectal cancer. However, observational studies provided acceptable evidence that colonoscopy screening is the only effective screening strategy for colorectal cancer in LS and reduced mortality and the incidence of colorectal cancer.

- Differential diagnosis of LS (family history, histology, computational model, etc.) lacks sensitivity and specificity to adequately identify LS individuals for colonoscopy screening. Genetic testing provides a definitive diagnosis for LS.
- Standard protocols for genetic testing are complex and vary, and best practice guidelines have not been established. Costs of genetic testing may, therefore, differ significantly according to the series of tests performed, performance standards, laboratory protocols, costs of resources, etc. Generalisability of published data to varying settings is, therefore, challenging and often not possible.
- Timing of an economic evaluation is critical as genetic testing technology evolve continuously.
- Generally, genetic testing do not impact directly on health outcomes that are important for a service provider (e.g. mortality or morbidity), but inform on further management of a patient. Thus, it is important to include the costs of the both the genetic testing and the intervention (e.g. colonoscopy) in an economic analysis.
- Cascade genetic testing i.e. testing of a relative is less costly than diagnosing a proband; and the benefit for the relative may be greater as he / she may not have cancer yet. Thus, cascade testing reflects the benefit of genetic testing and has to be considered when assessing costs and benefits.
- Long-term, colonoscopies contribute to the majority of the costs of screening for colorectal cancer. Parameters that influence the number of colonoscopies in the screening process include discount rates, adherence to colonoscopy and positivity rate of relatives.
- No published local study involved the economic aspects related to providing a colonoscopy screening service for Lynch Syndrome.

11. Conclusion

An overview of the literature indicated that publications focused predominantly on high income countries which are not generalisable to South Africa. A number of evidence-based guidelines and one detailed health technology assessment provided best practice evidence as well as cost-effectiveness data. Though these publications provided guidance on recommended practices, practices in South Africa differ due to availability of resources, skills and equipment. Grosse et al. (2008) recommended that in order to inform appropriately on cost-effectiveness for screening for LS, unlike most of these studies where a number of assumptions are applied, actual real-life clinical practice should be documented. The aim of our study, therefore, is to estimate from actual expenditure and utilisation data, the costs of implementing screening options for colorectal cancer for patients with LS.

References

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., et al. 2011. Cancer risks associated with germline mutations in MLH1, MLH2 & MLH6 genes in Lynch Syndrome. *JAMA.* 305:22, 2304-2310.

Bruwer, Z., Futter, M., Ramesar, R. 2013. A mobile colonoscopic unit for Lynch Syndrome: Trends in surveillance uptake and patient experiences of screening in a development country. *J Genetic Council*. 22: 125-137.

Bruwer, Z., Futter, M., Ramesar, R. 2013. Communicating cancer risk within an African context: Experiences, disclosure patterns and uptake rates following genetic testing for Lynch Syndrome.*Patient Educ Couns*. 4469, 1-8.

Buchanan, J., Wordsworth, S., Schuh, A. 2013. Issues surrounding the health economic evaluation of genomic technologies. *Pharmacogenomics*.14:15, 1833-1847.

Coetzee, E. 2013. Early detection of colorectal cancer. *CME*. 31:6, 210 – 212.

Coetzee, E., Thompson, S.R. 2013. Inherited colorectal cancer: A plea for a national registry. *SAJS*. 51:2, 42-43.

Cohen, S.A., Leininger, A. 2014. The genetic basis of Lynch Syndrome and its implications for clinical practice and risk management. *The Application of Clinical Genetics*. 7, 147-158.

Day, L.W., Siao, D., Inadomi, J.M., Somsouk, M. 2014. Non-physicians performing lower and upper endoscopy: A systematic review and meta-analysis. *Endoscopy*. 46:5, 401-410.

Department of Health: Human Resource Department. 2015. Personnel Salary System (PERSAL) report for Groote Schuur Hospital establishment. Cape Town: Department of Health.

Department of Health. 2013. Guidelines for pharmacoeconomic submissions. Governement Gazette No. 36118. Pretoria: Government Printer

Department of Health: Western Cape Government. 2015. Hospital fees: Revision of the Uniform Patient Fee Schedule (UPFS) in respect of externally funded, foreigners, revenue generation projects and patients treated by their private practitioner: Effective 1 April 2015. Finance instruction FAR:1/2015. Cape Town: Department of Health.

Department of Health: National: Infrastructure Unit Support System Project. 2014. Order of magnitude estimator for new hospitals. Pretoria: National Department of Health.

Department of Public Service and Administration SA. 2015. Cost of living adjustment (COLA) 2015. Pretoria: Department of Public Service and Administration SA.

Division of Human Genetics: University of Cape Town. 2015. Standard operating procedures – Lynch Syndrome genetic testing. Cape Town: Division of Human Genetics: University of Cape Town.

Drummond, M.F., Sculpher M.J., Torrance, W.G., Brien, J.B., Stoddard. G.L. 2005. *Methods for the Economic Evaluation of the Health Care Programmes.* New York: Oxford University Press.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. 2009. Recommendations from the EGAPP Working Group: genetic testing strategies in

newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine.* 1: 1, 35-41.

Finance Department: Groote Schuur Hospital, 2015. Basic Accounting System (BAS) report. Groote Schuur Hospital

Giardiello, F.M., Allen, J.I., Axilbund, J.E., Boland, R., Burke, C.A., 4 , Burt, RW., Church, JM., Dominitz, J.A., Johnson, D.A., Kaltenbach, T., Levin, T.R., Lieberman, D.A., Robertson, D.J., Sapna Syngal, S., Rex, DK. 2014. Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US. Multi-Society Task Force on Colorectal Cancer. *The American Journal of Gastroenterology.* 147, 502-526.

Glick H.A, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. 2007. Oxford, Oxford University Press.

Graham, A., Adeloye, L.G., Theodoratou, E., Campbell, H. Estimating the incidence of colorectal cancer in Sub-Saharan Africa: A systematic analysis. *Journal of Global Health*. 2:2, 1-14.

Gray, A.M., Clarke, P.M., Wolstenholme, J.L., Wordsworth, S. 2012. *Applied Methods of Cost-effective Analysis in Health Care.* United Kingdom: Oxford University Press.

Groote Schuur Hospital Gastroenterology Department. 2011. Suggested standard operating procedure for detecting HNPC in a colorectal cancer sample at GSH. Cape Town: GSH Gastroenterology Department.

Grosse, S.D., 2015. When is genetic testing cost-effective? Testing for Lynch Syndrome in patients with newly-diagnosed colorectal cancer and their relatives. *Healthcare*. 3, 860-878.

Hampel, H., 2009. Genetic testing for hereditary colorectal cancer. *Surg Oncol clin N Am.* 18:4, 678.

Hedge, M., Ferber, M., Mao, R., Samowitz, W., Ganguly, A. 2014. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and *MYH*-associated polyposis). *Genetics in Medicine*. 16:1, 101-116.

Järvinen, H.J., Aarnio, M., Mustonen, H., Aktan-Collan, K., Aaltonen, L.A., Peltomäki, P., De La Chapelle, A., Mecklin, J.P. 2000. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 118:5,829-34.

Lynch, H.T., Snyder, C.L., Shaw, T.G., Heinen, C.D., Hitchins, M.P. 2015. Milestones of Lynch Syndrome: 1895-2015. *Nature Review*: *Cancer*. 15, 181-194.

Mangham, L. (2009) ACT Consortium Guidance on Economic Evaluation. Available at www.actconsortium.org/healtheconomicsguidance [20 July 2015]

National Department of Health: Sub-directorate Human Genetics. 2000. Human genetics policy guidelines for the management and prevention of genetic disorders, birth defects and disabilities. Pretoria: National Department of Health

National Health Laboratory Services. 2015. National Cancer Registry report 2009. National Institute for Occupational Health. http://www.nioh.ac.za [23 May 2015].

Palomaki, G.E., McClain M.R., Melillo, S., Hampel, H.L., Thibodeau, SN. 2009. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genetics in Medicine.* 11:1, 42-65.

Ruco, A., Walsh, C.M., Cooper, M.A., Rabeneck, L. 2016. Training non-physicians to do endoscopy: Feasibility, effectiveness and cost-effectiveness. *Best Practice & research Clinical Gastroenterology.* 30, 389-396

Sinanovic, E., Floyd, K., Dudley, V., Azevedo, V., Grant, R., Maher, D. 2003. Cost and cost-effectiveness of community-based care for tuberculosis in Cape Town, South Africa. *Int J Tuberc Lung Dis.* 7:9, 556-562.

Sinanovic, E., Kumaranayake, L. Sharing the burden of TB/HIV? Costs and financing of public–private partnerships for tuberculosis treatment in South Africa. *Tropical Medicne and International Health.* 11:9, 1466-1474.

Statistics South Africa. 2015. Mortality and causes of death in South Africa, 2014. Pretoria: Statistics South Africa

Snowsill, T., Huxley, N., Hoyle, M., Jones-Hughes, T., Coelho, H., Cooper, C., Fraylin, I., Hyde, C., 2014. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. *Health Technology Assessment.* 18, 58.

Somda, Z.C., Meltzer, M.I., Perry, H.N. 2007. SurvCost 1.0: a manual to assist country and district public health officials in estimating the cost of the implementation of IDSRS. CDCP. Department of Health and Human Services. USA.

Stupart, D.A., Goldberg, P.A., Algar, U., Ramesar, R. 2009. Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. *Colorectal Disease*. 11:2, 126-30.

Vasen, H.F.A., Blanco,I., Aktan-Collan, K., Gopie, J.P., Alonso, A., Aretz, S., Bernstein, I. (Mallorcca group). 2013. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut,* 62, 812–823.

Walker, D. & Kumaranayake, L. 2002. How to do (and not to do)… Allowing for differential timing in cost analysis: discounting and annualisation. *Health Policy and Planning*. 17:1, 112-118.

Wentwink, M.Q., Rakers, M., Stupart,D.A., Algar, U., Ramesar, R., Goldberg, P.A. Incidence and histological features of colorectal cancer in the Northern Cape province, South Africa. *SAJS*. 48:4, 109-113.

Wolf, A.I., Buchanan, A.H., Farkas, M.L. 2013. Historical review of Lynch Syndrome. *Journal of Coloproctology*. 2013:33:2, 95-110.

Vergouwe, F., Boutall, A., Stupart, D., Algar, U., Govender, D., Van der Linde, GD., Mall, A., Ramesar, R., Goldberg, PA. 2013. Mismatch repair deficiency in colorectal cancer patients in a low-incidence area. *SAJS*. 51:1, 16 -21.

PART C: JOURNAL ARTICLE

Full title:

A comparative cost analysis of two screening strategies for colorectal cancer in Lynch Syndrome in a tertiary hospital, South Africa

Short title:

Cost analysis of colorectal cancer screening in Lynch Syndrome, South Africa

Abstract

Aim: Individuals with Lynch Syndrome have a 25% to 75% lifetime risk of colorectal cancer and the cancer generally presents at an early age. It is, thus, important to establish the cost of strategies to prevent or delay the onset of cancer. Colonoscopy was the only screening method shown to be effective. This study compared the cost of two screening approaches - colonoscopy only (Strategy 1) versus genetic testing for Lynch Syndrome followed by colonoscopy for the individuals that tested positive (Strategy 2).

Method: A comparative cost analysis of two screening approaches was conducted from the health service perspective at a tertiary hospital. Probands that were selected for genetic testing between 01 November 2014 and 30 October 2015, and their relatives were analysed. From this cohort, all probands and their 1st degree relatives were analysed according to Strategy 1. From the same cohort, probands that tested positive for a mutation and their 1st degree relatives were analysed according to Strategy 2. Total costs for the two screening strategies were estimated and compared. Sensitivity analyses were performed on adherence rates to colonoscopy, positivity rates of relatives and discount rates.

Results: A total of 40 families were studied. The total cost for Strategy 1 amounted to R4 932 718 ($332 617) compared to R390 308 ($26 319) for Strategy 2 (Discount rate 3%; Adherence 75% and Positivity rate of relatives 45%). Base case analysis indicated a difference of 90% less in the total cost for Strategy 2 compared to Strategy 1. One-way sensitivity analyses showed that the difference in cost between the two strategies was not sensitive to changes in discount rates, adherence rates or positivity rates of relatives.

Conclusion: Colonoscopy screening for Lynch Syndrome and at-risk patients was substantially less costly when combined with genetic testing. Effectiveness of the screening programmes should be established through further research.

Key words: genetic testing, Lynch Syndrome, HNPCC, colorectal cancer, colonoscopy, cost-effectivenss

1. Introduction

In South Africa, colorectal cancer is the fifth most common cancer, with approximately 4 697 new cases and 3 138 deaths reported in 2012 (National Health Laboratory Services: Globocan, 2015). Just over half of the new cases diagnosed and 41% of deaths occurred in individuals younger than 65 years of age (National Health Laboratory Services: Globocan, 2015). The most common cause of hereditary colorectal cancer is Lynch Syndrome (LS) which accounts for approximately 3% to 5% of all colorectal cancers (Graham et al. 2012; Bonadona et al. 2011; Snowsill et al. 2014).

LS is clinically defined as a disorder that predisposes individuals to colorectal cancer, endometrial cancer and certain other cancers as a result of an underlying germline mismatch repair (MMR) gene mutation (Vasen et al. 2013). The disorder presents with high rates of multiple primary tumours, has an early age of onset and generally has an absence of typical risk factors (Vasen et al. 2013). Carriers of a mutation in any of the MMR genes have a lifetime risk for colorectal cancer of 25% to 75%, compared to a 5% lifetime risk in the general population (Cohen et al 2014; Giardiello et al. 2014; Snowsill et al. 2014; Vasen et al 2013). The highest risks, in the region of 40% to 70%, are associated with individuals with *MLH1* and *MSH2* mutations, with lower risks reported for *MSH6* (10% - 22%) and *PMS2* (15% - 22%) (Bonadona et al. 2011; Steinke et al. 2013; Vasen et al. 2013; Giardiello et al. 2014). LS-associated mutations have an autosomal dominant pattern i.e. if a parent carries the mutation then there is a 50% chance that the mutation will be passed on to the child (Snowsill et al. 2014).

Colorectal cancer is the most common cancer associated with LS (Snowsill et al. 2014; Vasen et al. 2013). Progression of adenoma to carcinoma is approximately five times more accelerated in individuals with LS compared to sporadic and familial colorectal cancers. Furthermore, colorectal cancer is generally asymptomatic until it has reached an advanced

stage (Snowsill et al. 2014; Vasen et al. 2013). As colorectal cancer has a relatively earlier onset in LS individuals than occurs in sporadic forms (Bonadona et al. 2011; Cohen, et al. 2014; Snowsill 2014), persons affected are usually economically active and support families. Thus, preventing or delaying cancer onset, would have social as well as economic benefits. An effective screening programme is fundamental for early detection and successful management of colorectal cancer (Snowsill et al. 2014; Vasen et al. 2013). Advantages of appropriate screening are the early detection of cancer and consequently improved chances of curative treatment; and the early detection of pre-cancerous lesions which allows for removal of the polyps before they can progress to cancer (EGAPP 2009; Giardello et al 2014). Colonoscopy is the only screening method that has proved to be effective for these individuals (Snowsill et al. 2014; Vasen et al. 2013). Studies conducted in high income countries have shown that effective colonoscopy screening programmes reduced mortality by 62% to 72% (Palomaki et al. 2009; Giardiello et al. 2014; Snowsill et al 2014). Stupart et al. (2009) showed an 80% decrease in mortality in a South African study, based on the communities which are the subjects of the present study. For the general population colonoscopy screening every five to ten years is recommended for individuals commencing from around 50 years old (Palomaki et al. 2009; Giardiello et al. 2014; Snowsill et al 2014). However, for LS-affected and at risk individuals biennial colonoscopy is recommended for persons from as young as 25 years old and annual colonoscopy is recommended for persons from 30 years to around 70 years old (Palomaki et al. 2009; Giardiello et al. 2014; Snowsill et al 2014).

In a resource-constrained environment, accurate prediction of individuals at high risk of colorectal cancer who will benefit from colonoscopy is intuitively desirable. Effective prediction will leave those at low risk of disease unexposed to the hazards of potentially invasive screening procedures, as well as optimise the use of scarce resources such as

equipment and skilled staff. Genetic testing to diagnose LS allows for identification of individuals at high risk of colorectal cancer (Snowsill et al. 2014).

The lack of genetic testing for LS and colonoscopy screening programmes in South Africa pose a major drawback for the management of colorectal cancer in individuals with LS. Also, unlike index screening colonoscopy, with genetic testing it is possible to determine if a patient has LS (Giardiello et al. 2014; Snowsill et al 2014). We, thus, hypothesised that genetic testing with colonoscopy screening will reduce the need for intensive colonoscopy on a large number of patients and consequently, reduce the cost of screening. Furthermore, determining the costs of these services is a key initial step to assessing affordability and successful implementation of such services. Thus far, no published study has assessed the cost implications of colonoscopy and genetic testing screening service for patients with LS in South Africa. Grosse et al. (2008) recommended that in order to inform appropriately on cost-effectiveness for screening for LS, actual real-life clinical practice should be documented. Published studies (Snowsill et al 2014; Grosse 2015) indicated that long-term, colonoscopy costs were the biggest cost drivers. Preventative measures (colonoscopy) exceeded the cost savings from the delayed management of cancer. In terms of genetic testing, costs for diagnosing a proband exceeded the cost for diagnosing a relative. Adherence to colonoscopy, uptake of genetic testing and positivity rates of relatives are the key parameters that influence total costs of colonoscopy programmes (Snowsill et al 2014; Grosse 2015).

This study estimated and compared the cost of two screening approaches – intensive colonoscopy only for individuals considered at an increased risk of LS (e.g. probands or their first degree relatives) versus genetic testing for LS of at risk individuals followed by intensive colonoscopy only for the individuals who tested positive.

2. Method

2.1 Study design and objectives

A comparative cost analysis from the health service perspective, using a micro-costing and ingredients-based approach was conducted. Costs were collected in 2015 and presented in the 2016 South African Rands and US Dollars. The unit costs for genetic testing and colonoscopy were estimated; and the total number of colonoscopies required for each strategy was projected. This information was utilised to estimate and compare the total cost for the two strategies.

2.2 Screening strategies

Two screening strategies for colorectal cancer were considered, based on what is currently available at GSH and the research interface with the Human Genetics Research Unit in the Division of Human Genetics at UCT. Both strategies were applied to the same study cohort and costed. Strategy 1 involved intensive colonoscopy screening for all patients with colorectal cancer who were suspected of having LS based on the Revised Bethesda Criteria, as well as their 1st degree relatives. Strategy 2 involved intensive colonoscopy screening only for probands and 1st degree relatives with a genetic test-confirmed diagnosis of LS. Individuals who were negative on germline testing were managed as per the general population i.e. colonoscopy every 10 years from the age of 50 years. Intensive colonoscopy screening involved biennial colonoscopy for patients under 30 years of age, and annual colonoscopy for individuals aged 30-60 years. Individuals older than 60 years were managed as per the general population i.e. colonoscopy every 10 years (Voster, A: Division of Human Genetics: UCT, personal communication 2015).

2.3 Setting and population

The study was undertaken at Groote Schuur hospital, a public sector tertiary hospital in Observatory in Cape Town that provides sub-specialist care. In South Africa, approximately 80% of the population seeks health care in the public sector (Department of Health, 2014). The study included individuals from the Western Cape and Northern Cape provinces. Subjects were recruited from the DNA and pedigree database (Ethics approval: HREC REF: 217/2010) in the Division of Human Genetics at the University of Cape Town (UCT).

In this study, a proband is defined as the first medically identified individual in a family affected with a disorder and serves as the starting position for the genetic study of the family. Probands captured on the database were selected according to the Revised Bethesda Criteria after presenting with colorectal cancer or other LS-associated cancer; and may or may not have LS (Voster, A: Division of Human Genetics: UCT, personal communication 2015). As genetic testing is evolving and becoming more affordable or available, different test strategies have been applied over the years. To ensure that the latest available genetic procedures / tests employed were used to estimate costs, analysis of data was limited to probands tested between 01 November 2014 and 31 October 2015. A total of 40 probands and 934 relatives (40 families) on the DNA database were analysed according to patient demographics and screening strategy 1 and 2 i.e. the two screening options were applied to the same 40 families and costed (For details of the analysis - see Part D: Appendices: S1 and S2 Figs). From the 40 families, only probands and their first degree relatives (FDRs) were identified to receive colonoscopy screening as per the two screening strategies. FDRs are parents, children or siblings of the proband. FDRs of LS positive individuals have a 50% chance of having the LS-mutation (Snowsill et al. 2014) and were thus selected as high risk. Furthermore, individuals <25 years, >60 years,

deceased, spouses and family of spouses were excluded as they would not be eligible for colonoscopy screening. For Strategy 2, individuals were also assessed according to the genetic test results and only LS-positive individuals were assessed in terms costs for Strategy 2. The genetic tests performed and the results thereof are illustrated in Part D: Appendices: S3 Fig. Test results were derived from the National Health Laboratory Services (NHLS) and the DNA database. Surgical procedures performed were obtained from patient medical records. Five patients that had total colectomies were excluded as their screening procedures would not be done by colonoscopy. The number of colonoscopies required per proband and per FDR up to the age of 70 years was projected per screening strategy, taking into account the actual age of the individual.

In summary, for strategy 1, a total of 146 individuals were identified as eligible for colonoscopy. The total number of colonoscopies per lifetime for the eligible individuals for Strategy 1 was estimated as 2 671. For strategy 2, all 40 probands received genetic testing and only LS-positive probands and their families were further analysed for eligibility for colonoscopy. Thus, for strategy 2, a total of 12 individuals were identified as eligible for colonoscopy and a total of 264 colonoscopies were estimated for the lifetime for these individuals.

2.4 Colonoscopy

Colonoscopy is a 30 to 60 minutes procedure performed in a dedicated, equipped room (Algar, U: Surgical Gastroenterology Unit: GSH, personal communication 2015). A colonoscope is inserted into the rectum, through the colon and as far as the caecum. Prior to the procedure, patients are given a special cleansing preparation to clear the bowel. Sedatives may be given for pain control and to relax the patient. An intravenous cannula is prepared in the event that patients may require intravenous fluid or medication. The patient's heart rhythm and blood pressure is monitored continuously. Post-colonoscopy,

the patient is kept in an observation area for one to two hours (Algar, U: Surgical Gastroenterology Unit: GSH, personal communication 2015).

2.5 Genetic testing procedures

The reflex genetic testing procedure followed by the Division of Human Genetics at UCT for diagnosing LS was applied in this study. A database of all colorectal patients operated on at GSH is maintained and any patient meeting the Revised Bethesda Criteria underwent genetic testing (Voster, A: Division of Human Genetics: UCT, personal communication 2015; Coetzee 2013). Where possible, Immunohistochemistry (IHC) testing was used routinely as a first line preliminary screening test. Negative staining for a specific gene on IHC testing suggested a mutation affecting the respective gene and an increased risk for LS. If the IHC showed presence of all genes, but a strong clinical suspicion existed (e.g. family history, or relatively young age at diagnosis), the patient would be offered Microsatellite Instability (MSI) testing. MSI testing was only provided on request as it is relatively expensive, labour intensive, and requires a skilled geneticist. IHC and MSI were provided by the NHLS. Germline testing was provided by NHLS and the Division of Human Genetics, UCT. Genetic testing encompassed DNA extraction from whole blood following venepuncture, followed by testing for the five common founder mutations, i.e. mutations known to affect large family communities in our environment. The founder mutations were resolved by:

(i) A polymerase chain reaction (PCR), amplifying the fragment of DNA carrying the site of the mutation; followed by a restriction enzyme digest, which will specifically recognise the mutated DNA sequence and cut it. The cut (mutation positive) and uncut (mutation negative) fragments are distinguishable on an agarose gel run in an electric field (Hedge et al 2013), or

(ii) PCR followed by direct Sanger sequencing – which produces a graphic read out showing the exact site of the mutation (Hedge et al 2013), or

(iii) Multiplex Ligation-dependent Probe Amplification (MLPA) which detects deletions/insertions of whole exons of the respective gene(s) (Hedge et al 2013).

Where a previously identified mutation that is not one of the founder mutations was suspected, Sanger sequencing was done and if positive, this was followed by another sequencing test on a separate day, and preferably on DNAs from a separate blood sample, for quality assurance purposes. Only on identification of the MMR gene mutation in the proband, would the at-risk relatives be offered genetic testing for the identified MMR mutation (predictive testing). BRAF V600E was not offered due to its technical complexity. A genetic counsellor provided counselling prior to and after genetic testing, as well as follow-up counselling with every colonoscopy performed. Informed consent was obtained prior to genetic testing (Voster, A: Division of Human Genetics: UCT, personal communication 2015; Coetzee, 2013).

In summary, IHC was performed on probands with suitable colon tissue available for this test (22 individuals). All 40 probands received screening genetic tests i.e. the Common Founder test (39 individuals) or a Sequencing test for those with a known family mutation that was not a founder mutation (one individual). Only probands with LS-positive screening tests (4 individuals) received quality assurance / confirmatory tests i.e. digestive test and / or another sequencing test. See Part D: Appendices: S3 Fig for the flow diagram of tests performed.

2.6 Cost analysis

Capital, overhead and personnel costs were computed in order to estimate the costs for colonoscopy and genetic testing. The costs for performing colonoscopy and genetic testing were identified, quantified (measured) and then valued (Drummond et al 2005; Gray 2012). (See Part D: Appendices: S1 Table to S4 Table for examples of allocation of costs).

The equivalent annual cost of capital items were estimated by annuitizing the initial capital expenditure using a discount rate of 3% (Drummond et al 2005; Glick et al. 2007; Mangham 2009). Annuitizing makes allowance for opportunity cost, depreciation and useful clinical life years of capital items. The following useful life-years were assumed - buildings: 30 years; major equipment: 5 to 10 years; furniture: 10 years; and small equipment: 1 – 5 years (Drummond et al 2005; Somda et al. 2007). For shared building areas, equipment and furniture, the proportion of total utility (e.g. proportion of colonoscopy patients or proportion of total time) was used to estimate costs. For the diagnostic laboratory equipment, an efficiency rate of 65% and 70% was applied. The *NDOH/CSIR/DBSA Order of Magnitude Estimator for New Hospitals* (Department of Health: National 2014) and architectural drawings (Department of Health: Public Works 2015) were used to obtain costs for building spaces. Construction firms provided costs for a diagnostic laboratory. Equipment costs were obtained from medical suppliers. Furniture items were identified from asset registers (Feb 2016) and the costs were derived from government contracts and suppliers. An 8% mark-up was allocated for maintenance of equipment (Rademeyer: Deputy Director: WCGH Department of Public Works, personal communication 2015. Building and land maintenance costs were included in the Overhead and Maintenance category.

The GSH Finance report (BAS report 2015/16) and the UCT Finance Department provided cost information for shared overheads such as electricity, laboratory costs, housekeeping, stationery, maintenance, etc. Proportions in terms of colonoscopy patients or floor space, as appropriate, were used to allocate shared overhead costs. Costs for managerial and administrative overheads were estimated from the GSH personnel report (PERSAL report 2015) and government salary packages (COLA: Appendix B to DPSA Circular 1 of 2015); and were allocated according to the proportion of GSH staff involved in colonoscopy.

For personnel costs, a unit cost (cost per minute) was determined by dividing the annual total cost to company (CTC) by the annual total working minutes of the staff member. This unit cost was multiplied by the total time utilised by the staff member to perform the required task to obtain staff costs. GSH personnel report (PERSAL report Nov 2015), government salary packages (COLA: Appendix B to DPSA Circular 1 of 2015) UCT staff salaries (UCT Finance Department) were used to value staff costs.

Shared consumables costs were allocated according to the proportion of ward patients who underwent colonoscopy, whereas consumables and pharmaceuticals that were not shared were valued in terms of the quantities used (Department of Health & Treasury Contract Circulars 2012 to 2017).

The average unit cost for colonoscopy was estimated by dividing the total annual costs for colonoscopy by the number of colonoscopies performed per annum.

Costs for genetic tests were obtained from the NHLS and certain genetic tests performed at UCT were calculated using the ingredients approach as noted above. The cost of genetic testing varied amongst patients depending on the type of test and the number of tests conducted on the patient. Thus, the unit costs for genetic testing were estimated by calculating the weighted average cost for genetic testing where the weighting was applied according to the proportion of patients that required a particular test or series of tests.

The estimation of costs was based on the assumptions that:

- individuals undergoing colonoscopy screening have mortality rates as per the general population (Statistics South Africa 2015), as mortality rates for LS individuals in our cohort were not available at the time of the study. This may reflect an overestimation of costs - see section 6: Limitations; and

- all persons selected for genetic testing would be willing to undergo genetic testing.

To compare programmes with differential timing of resource outlays, time preference needs to be considered as positive time preference is desirable because of opportunity costs; value of a dollar today versus the future, and uncertainty of the future. Thus, a discounting rate of 3% was applied to discount future costs to present value (Drummond et al, 2005). As major adverse events are rare and literature indicated that costs are not significantly affected by including or excluding major adverse events, (Palomaki et al. 2009; Grosse 2015), these were excluded from the study.

2.7 Sensitivity analysis

Uncertainties most relevant to the study included positivity rates of the predictive tests for relatives, adherence rates to colonoscopy and discounting rates. Based on literature, a discounting rate of 3% and an adherence rate of 75% were assumed for the base case in Strategy 1 (Drummond et al 2005; Grosse, 2015). According to the DNA database, 27% of relatives tested positive in 2015. However, literature indicated positive test rates of 39% to 50% in studies carried out in high income countries (Grosse, 2015). Sensitivity analysis was, therefore, performed on positivity rates of 30%, 45% and 50%. Adherence rates reported in studies ranged generally from 79% to 88% (Grosse, 2015). However, in a study conducted in South Africa for LS-diagnosed persons, adherence rates as low as 25% was reported (Bruwer et al, 2013). Thus, adherence rates of 85%, 75%, 50% and 25% were analysed. As discount rates applied are according to societal value judgements, and therefore subjective, Drummond et al (2005) recommended that sensitivity analysis be performed on discount rates employed commonly in literature. The Department of Health guidelines recommends a discount rate of 5% and requires that costs should also be

presented undiscounted (Department of Health; Government Gazette No. 36118). Hence, discount rates of 0% and 5% were used for the sensitivity analysis.

Approval was obtained from the University of Cape Town Human Research Ethics Committee (HREC REF: 781/2015) and the relevant Provincial Department of Health authorities. The study was self-funded and was conducted as part of the requirements to complete the degree for a Master in Public Health: Health Economics at UCT.

3. Results

Analysis of 40 probands and 934 relatives resulted in 146 individuals and 2 706 colonoscopies identified as per Strategy 1 and 12 individuals and 267 colonoscopies as per Strategy 2. Accommodating for the general population mortality rate, 2 671 colonoscopies were estimated for Strategy 1 and 264 colonoscopies were estimated for Strategy 2. The average age of persons in Strategy 1 and 2 were 38 years and 39 years, respectively. Just over 83% of persons in Strategy 1 and 100% in Strategy 2 required annual colonoscopy screening. For Strategy 1, the number of FDRs per proband was 2.93 and for Strategy 2, the number of FDRs per LS-positive individual was 2.75.

3.1 Cost Analysis

Table 1 shows the breakdown by category of costs for colonoscopy. Around 82% of the colonoscopy costs constituted staff (56%) and equipment (26%) costs. The rest of the costs contributed, individually, less than 4% towards the total cost of colonoscopy.

Table 1: Annual and unit cost by category for colonoscopy presented in 2016 Rand and US $

CATEGORY OF COST	ANNUAL COST (n =2347)		UNIT COST		% OF TOTAL COST
	Rand	US $	Rand	US $	
Staff	4 464 949.62	301 075.50	1 902.41	128.28	56.05%
Equipment	2 106 100.49	142 016.22	897.36	60.51	26.44%
Building (Construction)	280 419.00	18 908.90	119.48	8.06	3.74%
Consumables	275 891.06	18 603.58	117.55	7.93	3.46%
Overheads & Housekeeping	273 704.01	18 456.10	116.62	7.86	3.44%
Laboratories	232 029.87	15 645.98	98.86	6.67	2.91%
Hospital Admin Services	162 109.41	10 931.18	69.07	4.66	2.03%
Pharmaceuticals	79 701.31	5 374.33	33.96	2.29	1.00%
Laundry & Linen Services	53 175.99	3 585.70	22.66	1.53	0.67%
Furniture Colonoscopy	13 913.84	938.22	5.93	0.40	0.17%
Furniture Shared	6 927.06	467.10	2.95	0.20	0.09%
TOTAL	**7 966 400.18**	**537 181.40**	**3 394.29**	**228.88**	**100.00%**
Follow-Up Genetic Counselling (Applicable to Strategy 2 only)	----	----	89.80	6.06	2.73%
TOTAL	**7 966 400.18**		**3 484.09**	**234.94**	**100.00%**

Table 2 presents the genetic counselling costs. About 69% of the genetic counselling costs were due to the initial outlay for genetic testing, while 31% of the costs were due to the follow-up counselling over the lifetime colonoscopy screening period.

Table 2: Costs of genetic counselling for diagnosing Lynch Syndrome for probands and their 1st degree relatives presented in 2016 Rand and US $.

GENETIC COUNSELLING	COST PER PATIENT		NUMBER OF PATIENTS / FOLLOW-UP COLONOSCOPIES	TOTAL COST		% OF TOTAL COST
	Rand	US $		Rand	US $	
ONCE-OFF GENETIC COUNSELLING SESSIONS FOR DIAGNOSING LS						
#Average cost of counselling of proband(s)	579.21	39.07	40	23 168.40	1 562.27	58.92%
#Average cost of counselling of relative(s)	373.49	25.18	11	4 108.39	277.03	10.45%
FOLLOW-UP GENETIC COUNSELLING SESSIONS WITH COLONOSCOPY SCREENING PROCEDURE						
*Follow-up (F/U) Counselling	89.90	6.06	**80 to 134	7 192.00 to 12 046.60	484.96 to 812.31	30.63%
TOTAL COST OF GENETIC COUNSELLING		--------	---------	**34 468.79 to 39 323.39**	**2 324.26 to 2 651.61**	**100.00%**

#includes pre- and post-test counselling, pedigree documentation and referral

*Assumption – 30% to 50% of relatives tested positive

A total of 22 patients had three IHC tests performed per individual i.e. for *MLH1*, *MSH2* and *MSH6* at a cost of R385 ($25) per test. Thus, a total of 66 IHC tests were performed

which amounted to R25 401 ($1 712). No MSI testing was done on any of the patients in the cohort.

The costs for genetic testing for diagnosing probands and their FDRs are shown in Table 3. Common founder mutation tests (screening) were performed on 39 probands. Restriction enzyme digest tests and sequencing tests (quality assurance) were performed on the three patients that tested positive with the common founder test. One proband with a suspicion of a known mutation that was not a founder mutation was diagnosed using sequencing testing for both screening and confirmatory purposes. The total costs for diagnosing all probands amounted to R107 940 ($7 279). Of this cost, 92% was due to the common founder mutation test cost. The weighted average unit cost per proband for confirming diagnosis of LS was R2 698 ($182) whereas the cost to test a relative for a known mutation was R926.12 ($62.45).

Table 3: Cost of genetic testing for diagnosing Lynch Syndrome in probands and their 1st degree relatives presented in 2016 Rand and US $.

GENETIC TESTS	COST PER TEST		NUMBER OF TESTS	TOTAL COST	
	Rand	US $		Rand	US $
DIAGNOSING LYNCH SYNDROME IN PROBANDS (n=40)					
Common Founder Mutation	2 534.54	170.91	39	98 847.06	6 665.34
Digest/Predictive	926.12	62.45	3	2 778.36	187.35
Sequencing	1 263.04	85.17	5	6 315.20	425.84
TOTAL			47	**107 940.62**	**7 278.53**
WEIGHTED AVERAGE UNIT COST to diagnose a proband	2 698.52	181.96			
DIAGNOSING LYNCH SYNDROME IN 1st DEGREE RELATIVES (n=11)					
Digest/Predictive	926.12	62.45	11	**10 187.32**	**686.94**

A summary of the total costs for conducting genetic testing for the study cohort is shown in Table 4. About 78% (63% for genetic testing + 15% for IHC) of the genetic testing costs were attributable to the tests to diagnose the proband. The predictive testing for the 1st degree relatives only contributed 6% to the total genetic testing costs. The total cost of

R170 805 ($11 517) was the once-off outlay to identify four LS patients and 11 FDRs in this cohort. This cost was constant for all scenarios with different parameters in Strategy 2.

Table 4: Costs by category of genetic testing procedure for diagnosing LS in probands tested between 01 November 2014 to 30 October 2015 and their 1st degree relatives, presented in 2016 Rand and US $

GENETIC TESTING DIAGNOSTIC PROCEDURES	NUMBER OF TESTS	UNIT COST		TOTAL COST		% OF TOTAL COST
		Rand	US $	Rand	US $	
IHC (Preliminary test)	66	384.86	25.95	25 400.76	1 712.80	14.87%
Ddiagnosing LS in probands	40	2 698.52	181.96	107 940.62	7 278.53	63.20%
Diagnosing LS in relatives	11	926.12	62.45	10 187.32	686.94	5.96%
Counselling (Excl F/U Counselling)	*112 sessions	4.49/min	0.30/min	27 276.79	1 862.00	15.97%
TOTAL	-----		-----	**170 805.49**	**11 517.56**	**100.00%**

*Sessions ranged from 15 minutes to 90 minutes (112 sessions = 6075mins)

Costs for the two screening strategies are reflected in table 5. The average unit cost for the entire genetic testing process to diagnose a proband (IHC, genetic testing, counselling) was estimated as R3 913 ($264). The average unit cost for the entire genetic testing process for diagnosing an FDR (genetic testing and counselling) was estimated as R1 300 ($88). The total cost for Strategy 2 was 92% less than the total cost for Strategy 1, i.e. R 390 308 ($26 318) at discount rate 3% and adherence 75% compared to R4 932 718 ($332 617) at discount rate 3%, adherence rate 75% and positivity rate of relatives 45%.

Table 5: Total cost per screening strategy based on utilization, presented in 2016 Rand and US $

CATEGORY OF COST	UNIT COST		QTY	TOTAL COST			
				STRATEGY 1		STRATEGY 2	
	Rand	US $		Rand	US $	Rand	US $
Colonoscopy	3 394.29	228.88	2 671	9 066 148.59	611 338.41	--	
Colonoscopy with genetic counselling	3 484.09	234.94	264	--		919 799.76	62 022.91
Genetic testing cost - proband	3 912.74	263.84	40	--		156 509.60	10 553.58
Genetic testing cost - relatives	1 299.61	87.63	11	--		14 295.71	963.97
TOTAL				**9 066 148.59**	**611 338.41**	**1 090 605.02**	**73 540.46**
***TOTAL COST + ASSUMPTIONS**				**4 932 718.04**	**332 617.53**	**390 308.54**	**26 318.85**

*Assumptions: Strategy 1 - Discount rate 3%; Adherence rate 75%; Strategy 2 - Discount rate 3%; Adherence rate 75%, Positivity rate of relatives 45%

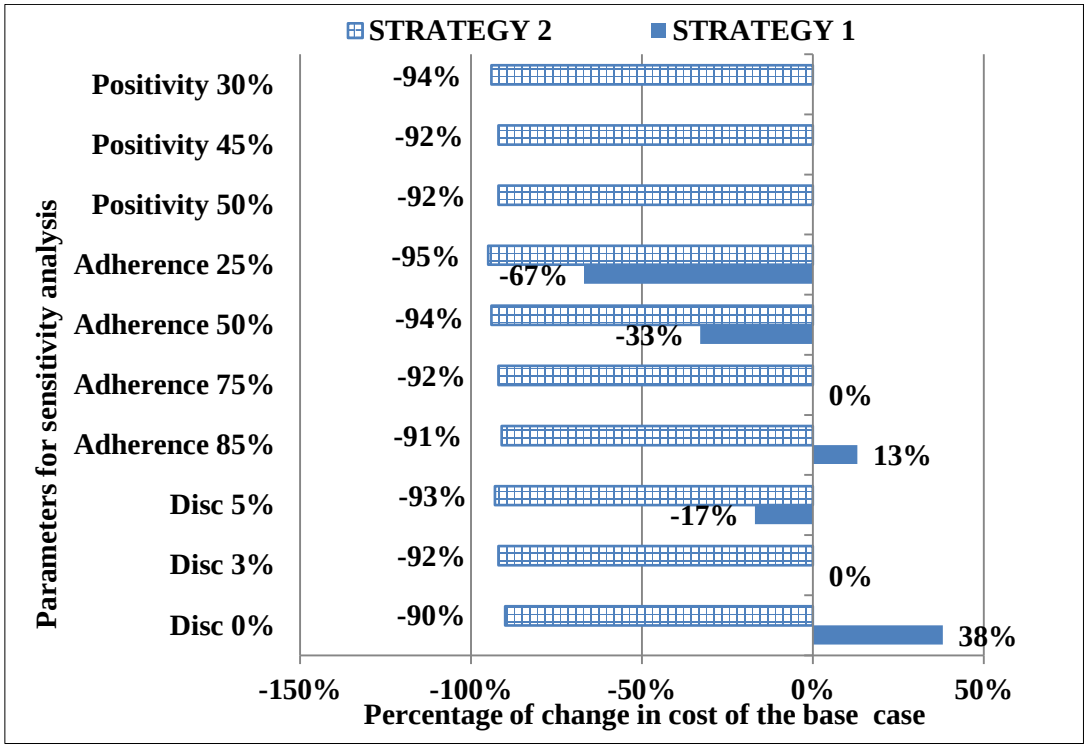
3.2 Base Case Analysis

According to scenarios reported in literature, the base case was defined as colonoscopy screening only (Strategy 1) with an adherence rate of 75% and a discount rate of 3% (Snowsill et al 2014; Grosse 2015). The total cost for the base case amounted to R4 932 718 ($332 618). The base case was compared with all combinations of the following parameters: discount rates of 0%, 3%, and 5%; adherence rates of 25%, 50%, 75% and 85%; and positivity rates of relatives of 30%, 45% and 50% (see Part D: Appendices S5 Table). Irrespective of the combination of parameters applied to Strategy 2, the costs for Strategy 2 remained between 89% and 96% less than the base case (Strategy 1). Additionally, with the lowest adherence rate (25%) applied to Strategy 1 and the highest adherence rate 85% and positivity rate of relatives of 50% applied to Strategy 2, Strategy 2 still remained less costly.

3.3 Sensitivity Analysis

One-way sensitivity analysis was conducted to assess the influence of the various parameters on the cost difference between the two screening options. Figure 1 depicts the adherence rates, discount rates and positivity rates of relatives on the difference in cost estimates from the base case. The differences in cost estimates between the two strategies were not significantly sensitive to any of the parameters applied. The cost difference for Strategy 2 remained between 90% and 95% less than the cost estimates for Strategy 1.

Figure 1: Impact of discount rates, adherence rates and positivity rates of relatives on the cost difference between Strategy 1 and Strategy 2



Difference in cost was measured against the base case. The base case is indicated as 0% on Figure 1.
Discount rate analysis (Constant parameters: Adherence rate 75% & Positivity rate 45%)
Adherence rate analysis (Constant parameters: Discount rate 3% & Positivity rate 45%)
Positivity rate analysis (Constant parameters: Discount rate 3% & Adherence rates 75%)

4. Discussion

This study has produced evidence that, for potential LS individuals and manifesting-LS individuals, colonoscopy screening with genetic testing (Strategy 2) is substantially less costly than offering colonoscopy screening only (Strategy 1). The total cost for Strategy 2 was 92% less than the total cost for Strategy 1, i.e. R390 308 ($26 319) compared to R4 932 718 ($332 617). The base case analysis and one-way sensitivity analysis showed that this vast cost difference between Strategy 1 and 2 was not influenced by changes in discount rates, adherence rates and positivity rates of relatives. Strategy 2 also allows for high risk individuals to be identified to receive colonoscopy and thus, resources would be focused appropriately. In addition, low risk individuals would not be exposed to hazardous, invasive procedures unnecessarily. Furthermore, patients in this cohort tested positive for

MLH1 and *MSH2* mutations and the highest risks for cancer (40% to 70%), are associated with individuals with mutations in these two genes (Bonadona et al. 2011; Steinke et al. 2013; Vasen et al. 2013; Giardiello et al. 2014).

The Numbers Needed to Treat (NNT) for identifying a mutation in a proband was 10. Thus, to identify one patient it would cost R39 127 ($2 638) once off. We can translate this as R39 127 ($2 638) to exclude nine patients from the physical, psychological and financial implications of lifetime colonoscopy screening; while identifying the correct person who will benefit from colonoscopy. Furthermore, the cost of R39 127 ($2 638) for genetic testing would be offset easily by the savings incurred by not performing lifetime colonoscopies for nine patients. Similarly, the NNT for FDRs would range from 2 (50% positivity) to 3 (30% positivity). Thus, to identify one positive relative would cost between R2 600 ($175) to R3 900 ($262). This cost would exclude one in every two FDRs tested to one in every three FDRs tested from lifetime colonoscopy screening. Though the initial outlay to identify a mutation in a proband is high, the benefits for the relatives are acquired at a much lower cost.

The common founder genetic test made up 91% of the costs of identifying a mutation in a proband and about 63% of the overall costs for the genetic testing procedure. Influencing the price of the common founder test would significantly influence the total cost of genetic testing. The number of colonoscopies was the cost driver in the screening process for Strategy 1 and this was influenced by adherence to colonoscopy screening. For Strategy 2, the cost driver(s) (genetic testing and / or number of colonoscopies) were influenced by adherence to colonoscopy as well as the proportion of relatives that tested positive. The total cost for genetic testing for the cohort was fixed at R170 805 ($11 518). At a mutation positive rate of relatives of 45% and an adherence of 75%, genetic testing contributed 44% and colonoscopy 56% to the total costs; whereas at a mutation positive rate of relatives of

30% and adherence of 25%, genetic testing contributed 78% and colonoscopy 22% to total costs. This shows that the fewer the colonoscopies, the greater the proportion of the cost for genetic testing. Genetic testing without colonoscopy screening provides no benefit in reducing the risk of colorectal cancer and therefore would be a waste of resources. Thus, the less colonoscopies performed, the greater the proportion of loss in benefit of the total cost. Uptake of colonoscopy screening amongst mutation carriers were reported as around 79% to 88% in studies performed in high income countries (Grosse, 2015). However, a South African study reported adherence rates for LS-diagnosed persons of 25% over a 5 year period (Bruwer et al., 2013). As access to colonoscopy screening in South Africa is generally limited to tertiary care hospitals in the public sector, this may be one of the reasons for the low adherence rate. A well-functioning, accessible colonoscopy programme is, therefore, important in order to optimise the benefits of genetic testing.

Literature reported that the proportions of FDRs that tested positive for a mutation ranged from 39% to 50% (Grosse, 2015; Snowsill 2014). Also, family mutation prevalence in FDRs is assumed at 50% due to autosomal dominant inheritance of LS (Grosse, 2015). The proportion of relatives on the DNA database that tested positive for a mutation in 2015 was 27%. This may be an under detection of mutations as the Division of Human Genetics: UCT test predominantly for founder mutations in *MHL1* and *MSH2* genes. Also, genetic testing in the public sector is not an established practice and many relatives may not have the opportunity to get tested. The greater the proportion of positive relatives identified to the proband, the greater the benefit of genetic testing as predictive testing is less expensive than diagnosing a proband and the relative is more likely to be ‘at risk’ (i.e. not affected by cancer yet). Thus, to improve the benefit / value for money of a genetic testing programme, testing of relatives should be strongly encouraged and facilitated.

Staff executing colonoscopy contributed 56% to the total cost of colonoscopy. In the Western Cape colonoscopies are performed by sub-specialists and this significantly inflates the cost of colonoscopy. Furthermore, the demand for colonoscopy outweighs the supply of gastroenterologists. Data exists for non-physicians providing simple endoscopy procedures safely and effectively (Day et al, 2014); however, published data on non-physician colonoscopy programmes is lacking (Ruco et al, 2016). This emphasises the importance of selecting appropriate persons for colonoscopy screening and avoiding unnecessary colonoscopies. An annual cost of R3 484 ($235) per patient for colonoscopy can be translated to about R290 ($20) per month to reduce the risk of colorectal cancer by 62% to 72% (Palomaki et al. 2009; Giardiello et al. 2014; Snowsill et al 2014; Gross, 2015). Compared with other tertiary treatments, this does not appear excessive. Conclusive evidence on whether colonoscopy screening every 1 to 2 years is superior to 2 to 3 years has not been established (Grosse, 2015; Vasen et al. 2013). Employing biennial colonoscopy would reduce the total cost of colonoscopies by almost half in both strategies as more than 80% of individuals in Strategy 1 and 100% individuals in Strategy 2 formed part of the annual colonoscopy regimen.

Our study assumed that all persons identified for genetic testing would accede to testing. Based on this assumption, the number of FDRs tested per proband was 2.75 which is consistent with data reported in literature (Grosse 2015; Snowsill et al 2014). In addition, Bruwer et al. (2013) reported high uptake rates of 97% and 74% for siblings and children, respectively. Furthermore, predictive genetic testing of FDRs contributed only 6% to the total costs of genetic testing. Thus, the uptake for genetic testing would not significantly affect the total cost for Strategy 2.

The cost of repeat colonoscopy, polypectomy, bleeding and biopsy was included in the cost estimate of colonoscopy. Major complications such as perforations are rare and were

excluded (Palomaki et al. 2009; Grosse 2015). Grosse (2015) reported that differences in assumptions regarding complications as well as excluding complications had little influence on incremental cost effectiveness ratios (ICERS).

5. Conclusion

Colonoscopy screening for potential and confirmed LS patients were substantially less costly when combined with genetic testing. Implementing colonoscopy screening with genetic testing would, thus, support the efficient use of health care resources.

6. Limitations

There is potential for generalisability in the public sector across South Africa as practices, salary packages and procurement contracts are usually aligned. However, patient profiles may differ. The study assumed general population mortality rates and did not include risks of other rarer cancers that are part of the LS spectrum and therefore the costs may be overestimated. This assumption is not expected to affect the direction of the results as the incidence of other cancers would be higher in the LS-diagnosed group (Strategy 2) and thus potential increased mortality rate in this group. Furthermore, in a cost-utility study Snowsill et al. (2015) reported that costs of surveillance of gynaecological cancer and other cancers associated with LS were excluded due to the lack of evidence of effectiveness of surveillance in these cancers (Snowsill et al., 2015). Strategies that included MSI testing, BRAF V600E and MLPA were not evaluated. At the time of the study, Sanger sequencing was less costly than MLPA and was the test used for quality assurance. As MSI was not requested for this cohort, the cost impact of MSI is assumed to be minimal as it would be once-off and required infrequently. The results of the genetic testing indicated that *BRAF*

V600E would not have been of value as all *MHL1* genes had positive mutations. IHC testing identified mismatch repair mutations in *MSH6* in 2 individuals and these patients tested negative for the common founder mutations (screening test). This study has provided evidence of cost implications for genetic testing and colonoscopy screening; however, further research on the effectiveness of such programmes would be of value.

References

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., et al. 2011. Cancer risks associated with germline mutations in MLH1, MLH2 & MLH6 genes in Lynch Syndrome. *JAMA.* 305:22, 2304-2310.

Bruwer, Z., Futter, M., Ramesar, R. 2013. A mobile colonoscopic unit for Lynch Syndrome: Trends in surveillance uptake and patient experiences of screening in a development country. *J Genetic Council*. 22: 125-137.

Bruwer, Z., Futter, M., Ramesar, R. 2013. Communicating cancer risk within an African context: Experiences, disclosure patterns and uptake rates following genetic testing for Lynch Syndrome.*Patient Educ Couns*. 4469, 1-8.

Buchanan, J., Wordsworth, S., Schuh, A. 2013. Issues surrounding the health economic evaluation of genomic technologies. *Pharmacogenomics*.14:15, 1833-1847.

Coetzee, E. 2013. Early detection of colorectal cancer. *CME*. 31:6, 210 – 212.

Coetzee, E., Thompson, S.R. 2013. Inherited colorectal cancer: A plea for a national registry. *SAJS*. 51:2, 42-43.

Cohen, S.A., Leininger, A. 2014. The genetic basis of Lynch Syndrome and its implications for clinical practice and risk management. *The Application of Clinical Genetics*. 7, 147-158.

Day, L.W., Siao, D., Inadomi, J.M., Somsouk, M. 2014. Non-physicians performing lower and upper endoscopy: A systematic review and meta-analysis. *Endoscopy*. 46:5, 401-410.

Department of Health. 2013. Guidelines for pharmacoeconomic submissions. Government Gazette No. 36118. Pretoria: Government Printer

Department of Health: Human Resource Department. 2015. Personnel Salary System (PERSAL) report for Groote Schuur Hospital establishment. Cape Town: Department of Health.

Department of Health: Western Cape Government. 2015. Hospital fees: Revision of the Uniform Patient Fee Schedule (UPFS) in respect of externally funded, foreigners, revenue generation projects and patients treated by their private practitioner: Effective 1 April 2015. Finance instruction FAR:1/2015. Cape Town: Department of Health.

Department of Health: National: Infrastructure Unit Support System Project. 2014. Order of magnitude estimator for new hospitals. Pretoria: National Department of Health.

Department of Public Service and Administration SA. 2015. Cost of living adjustment (COLA) 2015. Department of Public Service and Administration SA. Pretoria.

Drummond, M.F., Sculpher M.J., Torrance, W.G., Brien, J.B., Stoddard. G.L. 2005. *Methods for the Economic Evaluation of the Health Care Programmes.* New York: Oxford University Press.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. 2009. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine.* 1: 1, 35-41.

Finance Department: Groote Schuur Hospital, 2015. Basic Accounting System (BAS) report. Groote Schuur Hospital

Giardiello, F.M., Allen, J.I., Axilbund, J.E., Boland, R., Burke, C.A., 4 , Burt, RW., Church, JM., Dominitz, J.A., Johnson, D.A., Kaltenbach, T., Levin, T.R., Lieberman, D.A., Robertson, D.J., Sapna Syngal, S., Rex, DK. 2014. Guidelines on Genetic Evaluation

and Management of Lynch Syndrome: A Consensus Statement by the US. Multi-Society Task Force on Colorectal Cancer. *The American Journal of Gastroenterology.* 147, 502-526.

Glick H.A, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. 2007. Oxford, Oxford University Press.

Gray, A.M., Clarke, P.M., Wolstenholme, J.L., Wordsworth, S. 2012. *Applied Methods of Cost-effective Analysis in Health Care.* United Kingdom: Oxford University Press.

Grosse, S.D., 2015. When is genetic testing cost-effective? Testing for Lynch Syndrome in patients with newly-diagnosed colorectal cancer and their relatives. *Healthcare.* 3, 860-878.

Hampel, H., 2009. Genetic testing for hereditary colorectal cancer. *Surg Oncol clin N Am.* 18:4, 678

Hedge, M., Ferber, M., Mao, R., Samowitz, W., Ganguly, A. 2014. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and *MYH*-associated polyposis). *Genetics in Medicine*. 16:1, 101-116.

Mangham, L. (2009) ACT Consortium Guidance on Economic Evaluation. Available at www.actconsortium.org/healtheconomicsguidance [20 July 2015]

National Health Laboratory Services. 2015. National Cancer Registry report 2009. National Institute for Occupational Health. http://www.nioh.ac.za [23 May 2015].

Palomaki, G.E., McClain M.R., Melillo, S., Hampel, H.L., Thibodeau, SN. 2009. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genetics in Medicine.* 11:1, 42-65.

Ruco, A., Walsh, C.M., Cooper, M.A., Rabeneck, L. 2016. Training non-physicians to do endoscopy: Feasibility, effectiveness and cost-effectiveness. *Best Practice & research Clinical Gastroenterology*. 30, 389-396

Statistics South Africa. 2015. Mortality and causes of death in South Africa, 2014. Pretoria: Statistics South Africa

Snowsill, T., Huxley, N., Hoyle, M., Jones-Hughes, T., Coelho, H., Cooper, C., Fraylin, I., Hyde, C., 2014. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. *Health Technology Assessment.* 18, 58.

Somda, Z.C., Meltzer, M.I., Perry, H.N. 2007. SurvCost 1.0: a manual to assist country and district public health officials in estimating the cost of the implementation of IDSRS. CDCP. Department of Health and Human Services. USA.

Stupart, D.A., Goldberg, P.A., Algar, U., Ramesar, R. 2009. Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. *Colorectal Disease*. 11:2, 126-30.

Vasen, H.F.A., Blanco,I., Aktan-Collan, K., Gopie, J.P., Alonso, A., Aretz, S., Bernstein, I. (Mallorcca group). 2013. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut,* 62, 812–823.

PART D: APPENDICES

A comparative cost analysis of two screening strategies for colorectal cancer in Lynch Syndrome in a tertiary hospital, South Africa

1. Supplementary material
    - Cost allocation and calculations tables
    - Analysis of probands and relatives
    - Base Case analysis table
2. Consent form
3. Letter of approval from Research Ethics Committee
4. Permission to proceed with research – Groote Schuur hospital
5. Change of title
6. Instructions for author for journal article

1. SUPPLEMENTARY MATERIAL – COST ALLOCATIONS AND CALCULATIONS

Examples of Allocation of Costs – MS Excel ® data collection and cost analysis tools

S1 Table: Example: Personnel costs estimation per unit (minute) for colonoscopy (or genetic testing)

Staff Rank	Annual CTC	No of working days per year: 22dysx12mths	Cost per day	Number of hours worked per day	Number of working minutes per day (8x60)	Unit cost: Cost per minute	Time spent on task	Total cost	Source Documents
Total annual shared staff cost for e23				Proportion factor: (number of colonoscopies/E23 pts visits)					
Total annual shared hospital management cost for e23				Proportion factor: (number of staff involved colonoscopy/number of hospital staff)					

S2 Table: Example: Estimation of building cost for colonoscopy (or genetic test)

Building area	Value	Proportion allocation	Estimated building cost of usable area	Annuitised cost (for 30yrs, rate 3%, factor 19.6)	Source for measurement & valuation	Cost per colonoscopy
Shared ward area (m^2)	Estimated building cost ($rand/m^2$)	Colonoscopy pts/ total ward pts				Cost / number of colonoscopies
Colonoscopy Usable Area	Estimated building cost ($rand/m^2$)	100%				
Laboratory area	Cost of lab	Proportion time used				Cost per tests

S3 Table: Example: Estimation of equipment cost for colonoscopy (or genetic test)

Description	Qty	Unit Cost	% usable time	Total costs	Working life, years	Annual discount rate 3%	Annual equivalent cost	Annual maintenance (8%)	Total annual cost	Cost per colonoscopy
Electrical Surgical Unit										Cost / number of colonoscopies
Olympus scope										
Centrifuge										

Apply 65% and 75% efficiency rate to genetic testing equipment.

S4 Table: Example: Estimation of consumables and reagents for genetic testing

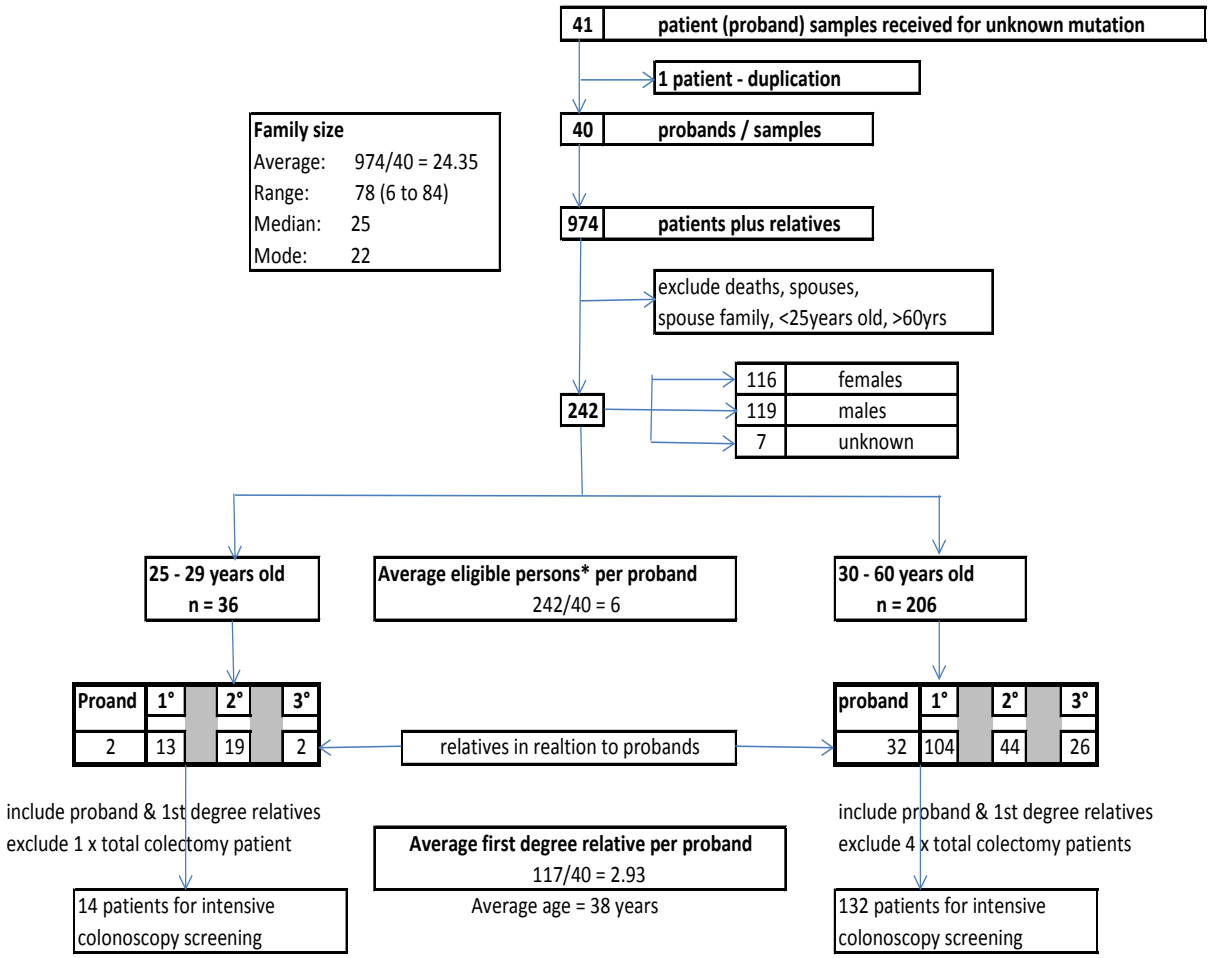
Item name	Original container qty (e.g. 5L; 500g)	Original container qty cost	Cost p/Unit	Qty Used for test	Cost p/test	No of Tests p/a	Total Cost p/a
Nuclease free H2O 1L							
100mM dNTP set							
Sense primer							
Antisense primer							

See Part A: Protocol – page 21 & 22

See Part C: Journal Article – page 10

2. SUPPLEMENTARY MATERIAL: ANALYSIS OF PROBANDS AND RELATIVES

S1 Fig: Demographic analysis per screening Strategy 1 of probands on the DNA database that were tested for LS between 01 November 2014 and 30 October 2015, and their relatives

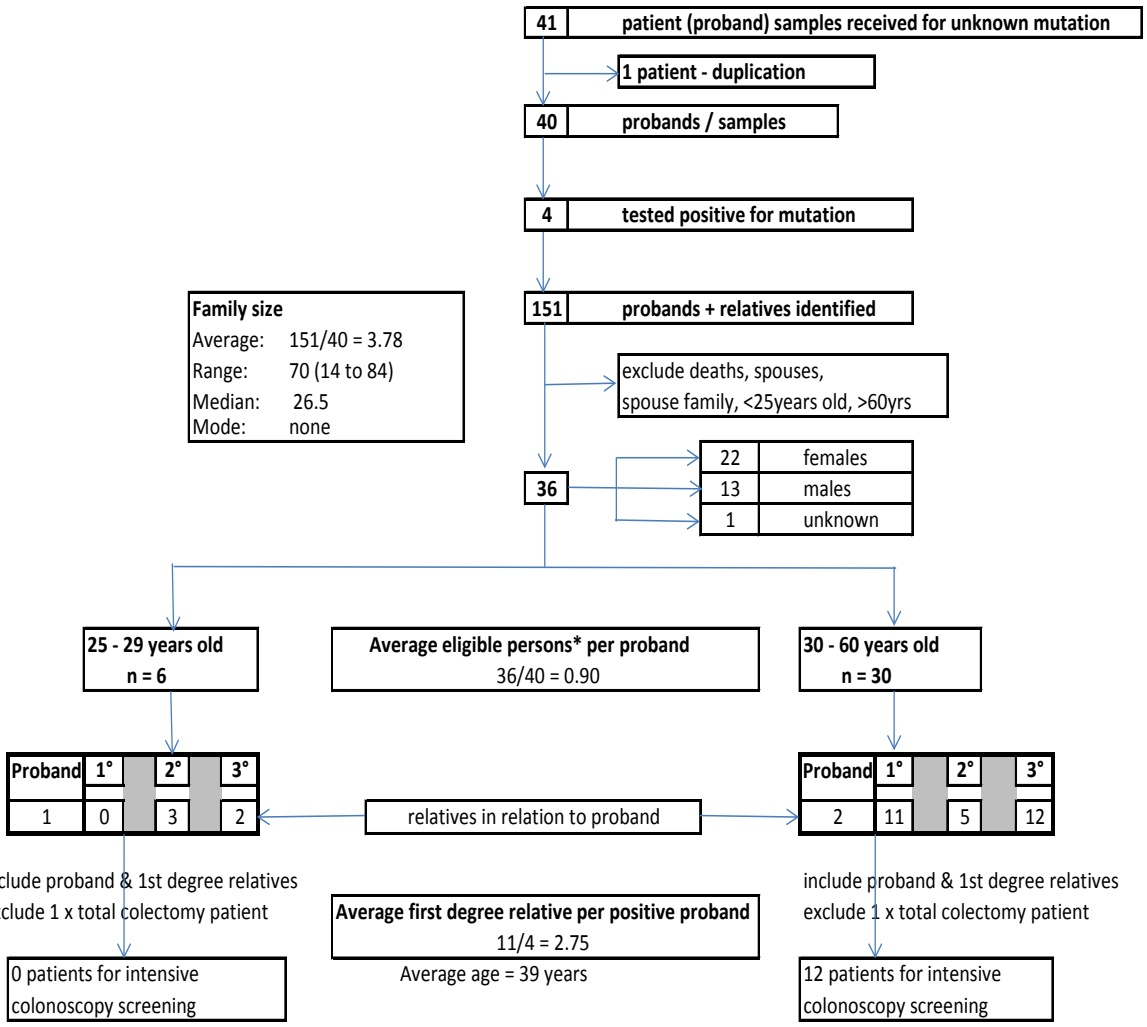


S1 Fig. illustrates the analysis for Strategy 1 of the probands and their relatives in terms of relationship, gender, age, etc. A total of 146 (14 +132) persons were selected for intensive colonoscopy.

See part A: Protocol – Pages 14, 15 & 17

See Part C: Journal Article – Page 7

S2 Fig: Demographic analysis per screening Strategy 2 of probands on the DNA database that were tested for LS between 01 November 2014 and 30 October 2015, and their relatives

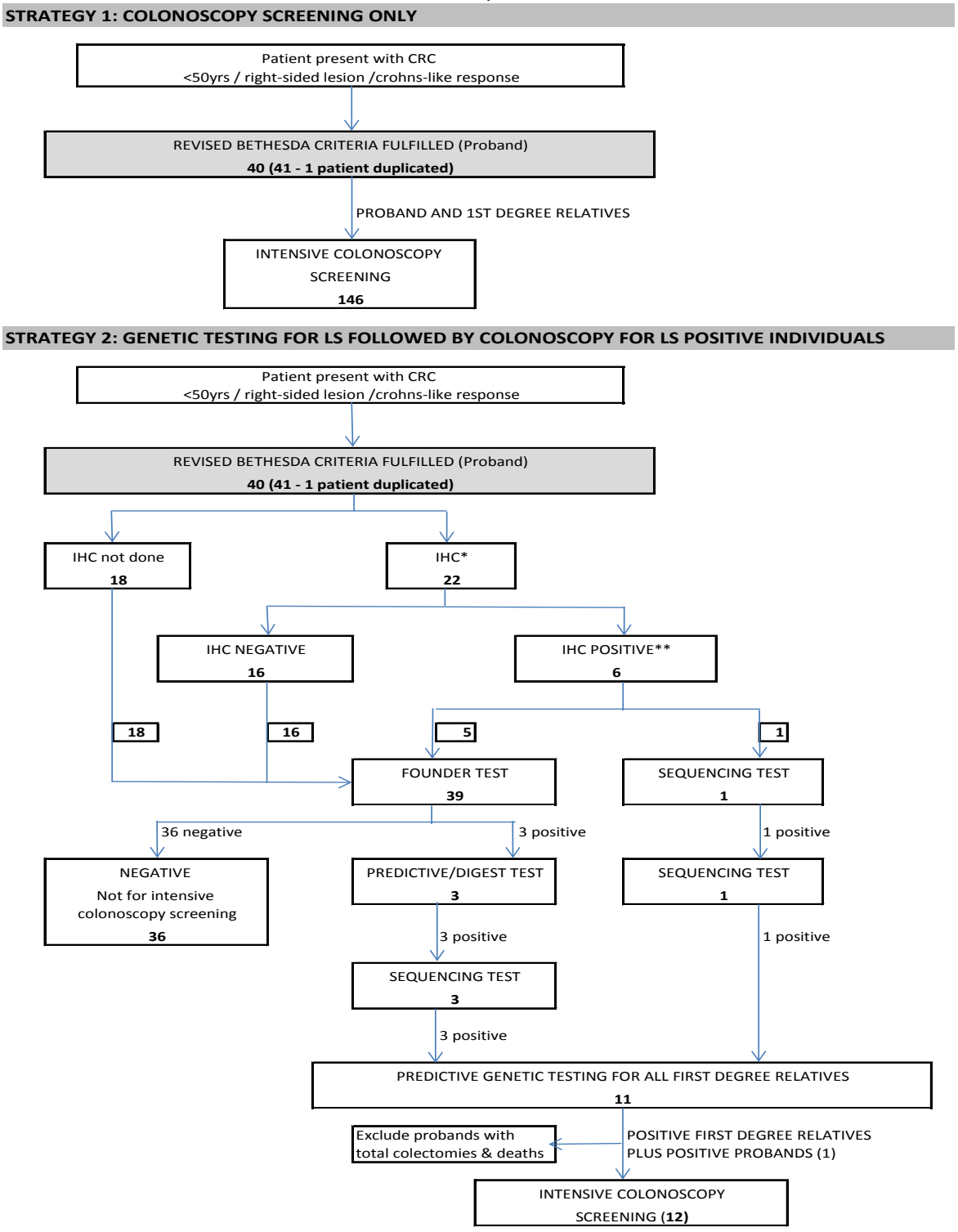


S2 Fig. illustrates the analysis for Strategy 2 of the probands and their relatives in terms of relationship, gender, age, etc. A total of 12 persons were selected for intensive colonoscopy.

See part A: Protocol – Pages 14, 15 & 17

See Part C: Journal Article – page 7

S3 Fig: Analysis per screening strategy of probands on the DNA database that were tested for LS between 01 November 2014 and 30 October 2015, and their relatives



CRC - Colorectal cancer
* includes 3 patients from the private sector - IHC assumed done
** 6 positive patients: 3 patients with MLH1 mismatch; 2 patients with MSH6 mismatch; 1 patientwith MSH2 mismatch (private sector)

S3 Fig: illustrates the analysis for Strategy 1 and 2 of probands in terms of the tests performed and the results; plus the relevant first degree relatives of the LS positive probands.

See part A: Protocol – Pages 14, 15 & 17 See Part C: Journal Article – page 8

S5 Table: Percentage difference in total costs of colonoscopy screening between the base case and Strategy 1 and 2 at various discount rates, adherence rates and positivity rates of relatives, presented in 2016 Rand and US $

DISCOUNT RATES	ADHERENCE RATE 85% % change in base case	ADHERENCE RATE 75% % change in base case	ADHERENCE RATE 50% % change in base case	ADHERENCE RATE 25% % change in base case
STRATEGY 1: COLONOSCOPY SCREENING FOR AT RISK PATIENTS				
No discount	56%	38%	-8%	-54%
Discount rate 3%	13%	¥**Base case 0%**	-33%	-67%
Discount rate 5%	-6%	-17%	-45%	-72%
STRATEGY 2: GENETIC TESTING AND COLONOSCOPY SCREENING FOR LS DIAGNOSED PATIENTS				
50% POSITIVITY RATE OF RELATIVES AT VARIOUS ADHERENCE RATES				
No discount	-89%	-90%	-92%	-94%
Discount rate 3%	-91%	-92%	-93%	-95%
Discount rate 5%	-92%	-93%	-94%	-95%
45% POSITIVITY RATE OF RELATIVES AT VARIOUS ADHERENCE RATES				
No discount	-89%	-90%	-92%	-94%
Discount rate 3%	-91%	-92%	-94%	-95%
Discount rate 5%	-92%	-93%	-94%	-95%
30% POSITIVITY RATE OF RELATIVES AT VARIOUS ADHERENCE RATES				
No discount	-92%	-92%	-94%	-95%
Discount rate 3%	-93%	-94%	-95%	-96%
Discount rate 5%	-94%	-94%	-95%	-96%

* Percentage change in base case: [(Cost of alternate case – Cost of base case) ÷ Cost of base case] x 100
¥ Base case: estimated at a discount rate 3%, adherence rate 75%

S6 Table shows that Strategy 2 (colonoscopy screening combined with genetic testing) costs between 89% and 96% less than Strategy 1 (colonoscopy screening only), irrespective of the scenario (parameters) applied. See Part C: Journal Article – pg 18.

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

A comparative cost analysis of two screening strategies for colorectal cancer in Lynch Syndrome in a tertiary hospital, South Africa.

PRINCIPAL INVESTIGATOR: Dr Edina Sinanovic, Director: School of Public Health & Family Medicine: Health Economics Unit, University of Cape Town (UCT), Anzio Road, Observatory.

CO-INVESTIGATOR / INTERVIEWER: Ms Yasmina Johnson (MPH: Masters Student), Pharmacy Services, 14th floor, 04 Dorp Street, Cape Town, 8001

CONTACT NUMBER: Office Hours: 021 483 6198 24 hour number: 084 417 5137

CO-INVESTIGATORS:

- Prof J Moodley, Cancer Research: Faculty of Health Science; and School of Public Health & Family Medicine, UCT, Anzio Road, Observatory
- Prof P Goldberg, Head: E22 Colorectal Unit, Groote Schuur Hospital, Observatory

I would like to invite you to take part in a research study. The details of the study are presented below. Please take some time to read the information which will enable you to decide whether you would like to participate or not.

It is very important that you understand what the research involves and how you will be involved in the research. If there is any part of the information / study that you do not understand clearly, please feel free to ask the person interviewing you to explain this to you.

Your decision to take part in the research is **entirely voluntary**. This means that you are free to decide not to participate and you may also withdraw from the study at any point during the study. You do not have to provide a reason for not participating or withdrawing from the study. If you decide not to take part in the study or to withdraw from the study, this will not affect you negatively in any way.

This study has been approved by the **Health Research Ethics Committee at the University of Cape Town** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

1. **Introduction**

Lynch Syndrome is a genetic disorder that increases an individual's risk to develop colorectal cancer and other cancers. Colorectal cancer is generally asymptomatic (no obvious symptoms present) until it has reached an advanced stage and thus an effective screening programme is important for early detection and successful management of colorectal cancer. Colonoscopy is the only screening programme that has proved to be effective for these individuals.

Furthermore, genetic testing allows for accurate prediction of individuals at high risk of colorectal cancer. Thus, using genetic testing, individuals at high risk who will benefit most from colonoscopy screening can be identified while those at low risk of disease can be excluded from potentially invasive screening procedures.

Preventing or delaying cancer onset, by appropriate screening strategies, will have social as well as economic benefits for the country. It is therefore important to establish the affordability of such a programme.

2. **What is this research study all about?**

The aim of the study is to estimate the cost of two screening options for colorectal cancer for individuals with a suspected or confirmed Lynch Syndrome diagnosis. Thus, information related to the cost of providing colonoscopy and genetic services will be collected and analysed.

3. **Why have you been invited to participate?**

You have been asked to participate in the study because you are involved in providing the service, have experience regarding the service or have access to information and costs related to the service.

4. **What will your responsibilities be?**

You will be asked to provide information regarding the logistics, utilisation, procedures or costs of providing the service.

5. **What will the investigator's / researcher's responsibilities be?**

The investigator / researcher will obtain formal permission to access and use the information that you provide as well as ethics approval. The researcher will organise suitable meeting times with you to obtain the study information.

6. How long will you be expected to participate in the study?

You may be expected to participate until 28 December 2016 when the study is anticipated to be completed. However, your involvement will only be related to the data noted in point 4.

7. Will you benefit from taking part in this research?

There will be no direct clinical benefit to you from participating in the study. However, the results of the study will inform policy-makers regarding affordability of the screening service, as well as providing insight into prioritising and allocation of resources.

8. Are there any risks involved in your taking part in this research?

No risks to you are anticipated as the research focuses on analysing data for costing purposes and no human subjects are directly involved.

9. Will you be paid to take part in this study and are there any costs involved?

You will not receive any payment for participating in the study. You will also not have any expenses while participating in the study. The study is self-funded by the researcher.

10. Who will have access to the information that you provide?

The study team will have access to the information that you provide. Regulatory authorities and members of the research ethics committee will have access to the information in order to check that the study was conducted properly.

Information will be captured under unique identifiers (codes) and no names will appear on forms or in the database. No identifiers will be used in the analysis or appear in any publication or report. All electronic data will be password protected and accessible only to the study team. Paper forms will be filed and stored in a locked cabinet.

Following completion of the study, it will be submitted for the Masters in Public Health: Health Economics degree. The findings of the study will also be submitted to the relevant Department of Health officials in the Western Cape, UCT Human Genetics department, Groote Schuur hospital and persons that participated in the study. A manuscript will be drafted for publication.

11. Is there anything else that you should know?

PART D: Appendices

- You can contact the researcher, Yasmina Johnson, at Tel 021 484-6198 or 084 415 7137 if you have any further queries or encounter any problems.
- You can contact the UCT Health Research Ethics Committee at 021-21 406 6492 if you have any concerns or complaints that have not been adequately addressed by the research team.
- You will be provided with a copy of this information and consent form for your own records.

12. Do you have any questions that you wish to ask?

DECLARATION BY INFORMANT / INTERVIEWEE:

By signing below, I ……..……. agree to take part in a research study entitled:
A cost analysis of providing colonoscopy screening versus colonoscopy screening plus genetic testing for adults with Lynch Syndrome in a tertiary level care hospital, South Africa.

I declare that:

- I have read and understood the information and consent form.
- I have had an opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that taking part in this study is **voluntary** and that I have not been coerced in any way to take part.
- I may choose to withdraw from the study at any time and will not be penalised or prejudiced in any way.

Signed at (*place*) .....….....…….. on (*date*) ……...…….

Signature of participant: _____

DECLARATION BY INVESTIGATOR:

I *(name)* ……..…… declare that:

- I explained the information in this document to ……
- I encouraged him/her to ask questions and took adequate time to explain and answer these questions.
- I am satisfied that he/she understands all aspects of the research adequately, as discussed in this information leaflet and consent form.

Signed at (*place*) .....….....…….. on (*date*) ……....……..

Signature of investigator: _____

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

26 November 2015

HREC REF: 781/2015

Dr E Sinanovic
Health Economics Division
School of Public Health & Family Medicine
FHS

Dear Dr Sinanovic

PROJECT TITLE: A COST ANALYSIS OF PROVIDING COLONOSCOPY SCREENING VERSUS COLONOSCOPY SCREENING PLUS GENETIC TESTING FOR ADULTS WITH LYNCH SYNDROME IN A TERTIARY LEVEL CARE HOSPITAL, SOUTH AFRICA.- Masters candidate Yasmina Johnson

Thank you for your response letter, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student:-Yasmina Johnson is also involved in this project.

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:781/2015

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail : *Bernadette.Eick@westerncape.gov.za*

Ms. Y. Johnson
Pharmacy Services
Western Cape Government Health
4 Dorp Street
CAPE TOWN
8001

E-mail: Yasmina.Johnson@westerncape.gov.za

Dear Ms. Johnson

RESEARCH PROJECT: A Cost Analysis of Providing Colonoscopy Screening Versus Colonoscopy Screening Plus Genetic Testing For Adults With Lynch Syndrome in the Western Cape, South Africa

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please introduce yourself to the person in charge of an area before commencing.
f) Please discuss the study with the HOD before commencing.
g) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
h) Confidentiality must be maintained at all times.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 10 December 2015
C.C. Mr. L. Naidoo
Professor E, Weimann
Professor S. Thomson

G46 Management Suite, Old Main Building,
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www.capegateway.go.v.za

D9 – Approval of Change of Title - 2015

University of Cape Town

Faculty of Health Sciences

Form D9: Approval for Change of Title

Please complete and return to Vuyi Mgoqi (Vuyi.Mgoqi@uct.ac.za) in the Postgraduate Office

Name and student no	Yasmina Johnson	JHNYAS001
Degree name (e.g. MSc(Med) in Physiology)	MPH: Health Economics	
Email address for correspondence	Yasmina.Johnson@westerncape.gov.za	
Student signature:		
Date:	08/02/2016	

Qualifications	B.Pharm
Old Title	A cost analysis of providing colonoscopy screening versus colonoscopy screening plus genetic testing for adults with Lynch Syndrome in a tertiary level care hospital, South Africa
Proposed new title	A comparative cost analysis of two screening strategies for colorectal cancer in Lynch Syndrome in a tertiary hospital, South Africa
Proposed title change supported by Departmental Research Committee (DRC)	Name of Chair, Department Research Committee: Alfred Jonckheere Signature: JHarner 16/2/2017

Please give reason for the need for to change your thesis/dissertation title:

Initial title is too long and complex. The new title is shorter and provides sufficient detail regarding the study.

(if you require more space than this then please attach a separate page)

I support / do not support the thesis/dissertation title change as requested by this student			
Supervisor name and signature:	Name: Prof Edina Sinamovic	Signature:	Date: 8 February 2017
I recommend / do not recommend the thesis/dissertation title change as requested by this student			
HOD name and signature	Name: Prof Mohamed Jeebhay	Signature:	Date: 15/02/2017
I approve / do not approve the thesis/dissertation title change as requested by the above student			
Deputy Dean: Postgraduate Affairs:	Name:	Signature:	Date:

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Received by:	Name:	Date:	
Captured on PeopleSoft	Name:	Date:	
Entered in DC	Name:	DC no: PG -med	Date:

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Font	Use a standard font size and any standard font, except for Symbol font.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers	Include page numbers and line numbers in the manuscript file.
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
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Nomenclature	Use correct and established nomenclature wherever possible.

Units of measurement	Use SI units. If you do not use these exclusively, provide the SI value in parent each value. Read more about SI units.
Drugs	Provide the Recommended International Non-Proprietary Name (rINN).
Species names	Write in italics (e.g., *Homo sapiens*). Write out in full the genus and species, b of the manuscript and at the first mention of an organism in a paper. After first first letter of the genus name followed by the full species name may be used (e
Genes, mutations, genotypes, and alleles	Write in italics. Use the recommended name by consulting the appropriate gen nomenclature database (e.g., HUGO for human genes). It is sometimes advisab the synonyms for the gene the first time it appears in the text. Gene prefixes su used for oncogenes or cellular localization should be shown in roman typeface MYC).

Manuscript Organization

Manuscripts should be organized as follows. Instructions for each element appear below the list.

Beginning section	*The following elements are required, in order:* • Title page: List title, authors, and affiliations as first page of manuscript • Abstract • Introduction
Middle section	*The following elements can be renamed as needed and presented in any order:* • Materials and Methods • Results • Discussion • Conclusions (optional)
Ending section	*The following elements are required, in order:* • Acknowledgments • References • Supporting information captions (if applicable)
Other elements	• Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately. • Tables are inserted immediately after the first paragraph in which they are cited. • Supporting information files are uploaded separately.

Parts of a Submission

Title

Include a full title and a short title for the manuscript.

Title	Length	Guidelines	Examples
Full title	250 characters	Specific, descriptive, concise, and comprehensible to readers outside the field	Impact of cigarette smoke exposure on innate immunity: A *Caenorhabditis elegans* model Solar drinking water disinfection (SODIS) to reduce childhood diarrhoea in rural Bolivia: A cluster-randomized, controlled trial
Short title	100 characters	State the topic of the study	Cigarette smoke exposure and innate immunity SODIS and childhood diarrhoea

Titles should be written in sentence case (only the first word of the text, proper nouns, and genus names are capitalized). Avoid specialist abbreviations if possible. For clinical trials, systematic reviews, or meta-analyses, the subtitle should include the study design.

Author List

Authorship requirements

All authors must meet the criteria for authorship as outlined in the authorship policy. Those who contributed to the work but do not meet the criteria for authorship can be mentioned in the Acknowledgments. Read more about Acknowledgments.

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PART E: POLICY BRIEF

A cost analysis of colorectal cancer screening in Lynch Syndrome, South Africa

Cost analysis of colorectal cancer screening in Lynch Syndrome, South Africa

Key messages

- Individuals with Lynch Syndrome (LS) have a high risk for colorectal cancer and the onset of cancer occurs at ages when persons are economically active and support families.
- South African families with LS have been implicated with the MMR genes, *MLH1* and *MSH2,* which presents the highest risks (40% to 70%) for colorectal cancer (Giardiello et al. 2014; Snowsill et al. 2014; Vasen et al. 2013).
- Colonoscopy reduced the incidence of colorectal cancer in individuals with LS by 62% and mortality by 65% to 70% (Palomaki et al. 2009; Vasen et al 2013; Snowsill et al. 2014).
- Colonoscopy screening combined with genetic testing significantly reduced the number of persons requiring intensive colonoscopy; and consequently was 92% less costly than performing colonoscopy screening only i.e. R4 932 718 ($332 617) compared to R390 308 ($26 319).
- This vast cost difference between the two strategies (colonoscopy only and colonoscopy + genetic testing) was not sensitive to discount rates, adherence rates or positivity rates of relatives.

Introduction

Lynch Syndrome, an autosomal dominant cancer syndrome, is associated with high risks for colorectal cancer, endometrial cancer and certain other cancers as a result of a mutation in one of the DNA mismatch repair (MMR) genes (Vasen et al. 2013). Mutation carriers have a lifetime risk for colorectal cancer of 25% to 75%, compared to a lifetime risk of 5%

in the general population (Bonadona et al. 2011; Giardiello et al. 2014; Snowsill et al. 2014; Vasen et al 2013). The highest risks are associated with *MLH1* and *MSH2* (40% to 70%), with lower risks associated with *MSH6* (10% to 22%) (Bonadona et al. 2011; Giardiello et al. 2014; Snowsill et al. 2014; Vasen et al 2013). The individuals included in this study were predominantly carriers of *MLH1* and *MSH2* mutations. Due to the autosomal dominant pattern, LS-associated mutations have a 50% chance of being passed on to a first degree relative (FDR) (Snowsill et al. 2014). FDRs (i.e. children, siblings or parents) of a mutation carrier are, therefore, considered as high risk for LS. Furthermore, colorectal cancers associated with Lynch Syndrome generally occur before the age of 50 years and thus, includes persons that are financially independent, economically active and support families (Snowsill et al. 2014). Thus, preventing or delaying cancer onset, by appropriate screening strategies, will have social as well as economic benefits for the country.

Colonoscopy is the only proven effective screening programme for colorectal cancer in LS; reducing colorectal cancer incidence by 62% and mortality by 65% to 70% (Palomaki et al. 2009; Vasen et al. 2013; Snowsill et al. 2014). Colonoscopy allows for (1) early detection of cancer and thus improved chances of curative treatment; and (2) pre-cancerous lesions to be removed before the polyps progress to cancer (EGAPP 2009; Giardello et al 2014). For LS, biennial colonoscopy (for individuals under 30 years old) and annual colonoscopy (for individuals between 30 years to 60 years old) were recommended (Snowsill et al. 2014; Vasen et al. 2013).

Due to limited resources in the public sector in South Africa, colonoscopies are generally reserved for patients that already present with symptoms. (Thomson: GIT clinic GSH, personal communication 2015). Identifying individuals at high risk of colorectal cancer who will benefit from colonoscopy screening and leaving those at low risk of disease

unexposed to potentially invasive screening procedures, will reduce the number of unnecessary colonoscopies; as well as direct the use of scarce resources more appropriately (Snowsill et al. 2014). Genetic testing for Lynch Syndrome is a cost-effective and reliable strategy to identify individuals for colonoscopy screening (EGAPP 2009; Snowsill, et al. 2014). Currently, genetic testing for LS is offered via a research interface with the University of Cape Town (Ramesar: Human Genetics UCT, personal communication 2014).

Colonoscopy screening and clinical genetics have a strong emphasis on prevention of cancers which supports the Western Cape Department of Health's strategic objective of enhanced wellness through primary, secondary and tertiary prevention (Department of Health: Western Cape. 2014). Furthermore, results from this study would inform on the development of the genetic services policy framework (Department of Health: Circular H212/2014) in terms of resource requirements and affordability of implementing an effective Lynch Syndrome genetic testing programme.

Published data on the cost implications associated with providing a formal colonoscopy and genetic testing screening service for patients with Lynch Syndrome in South Africa is not available. Studies conducted in high income countries are not generalisable to South Africa (Snowsill et al. 2014) as cost-effectiveness is context specific and linked to available resources. (Drummond et al. 2005). This study, therefore, estimated and compared the cost of two colonoscopy screening options for colorectal cancer from a health provider's perspective i.e. the cost of intensive colonoscopy for all LS and LS suspected individuals was compared to the cost of intensive colonoscopy only for individuals that tested positive for LS on genetic testing.

Objectives

- The average unit cost of colonoscopy was estimated.
- The average unit cost for genetic testing for diagnosing a proband and a relative with LS was estimated.
- The total numbers of colonoscopies required per strategy were projected.
- This information was utilised to estimate and compare the total cost for the two strategies.

Method

A comparative cost analysis of two screening approaches was conducted from the service provider perspective at a tertiary hospital. A total of 40 probands that fulfilled the Revised Bethesda Criteria and were selected for genetic testing between 01 November 2014 and 30 October 2015, and their relatives were assessed. From this cohort, all probands and their FDRs were analysed according to Strategy 1 (colonoscopy only). From the same cohort, probands that tested positive for a mutation and their FDRs were analysed according to Strategy 2 (genetic testing and colonoscopy). Total costs for the two screening strategies were compared. Sensitivity analyses were performed on adherence rates to colonoscopy, positivity rates of relatives and discount rates.

Key findings:

- Colonoscopy screening combined with genetic testing was 90% less costly than performing colonoscopy screening only i.e. R4 932 718 ($332 617) compared to R390 308 ($26 319). The cost difference between the two strategies was not influenced by discount rates, adherence rates or positivity rates of relatives.
- The unit cost of colonoscopy was R3 394.29 ($228.88); and with genetic counselling included it was R3 484.09 ($234.94).

- The weighted average unit cost for diagnosing a proband was R3 913 ($264) and for diagnosing a relative it was R1 300 ($88). The total cost for the cohort related to the genetic testing process was R170 805 ($11 518).
- It would cost R39 127 ($2 638) to exclude nine out of ten probands from the physical, psychological and financial implications of lifetime colonoscopy; while identifying one proband with confirmed LS.
- At a 50% positivity rate of relatives, it would cost R2 600 ($175) to exclude one FDR from lifetime colonoscopy while diagnose one FDR with LS. At a 30% positivity rate of relatives it would cost R3 900 ($262) to exclude two out three FDRs from lifetime colonoscopy; while identifying one FDR with LS.

Policy recommendations

- Implementation of a colonoscopy screening programme combined with genetic testing reduces the need for intensive colonoscopy on a large number of individuals; thus reducing the cost of colonoscopy screening. Also, a large number of low risk individuals would be saved from exposure to the physical and psychological hazards of colonoscopy.
- Colonoscopy services should be effective and accessible as genetic testing offers limited benefit without a well-functioning colonoscopy screening service.
- Genetic testing of relatives is less costly than diagnosing a proband and may be of greater benefit as the relative is more likely not to have cancer. Testing of relatives should, therefore, be strongly encouraged and accessibility to genetic testing services should be facilitated.
- Research with regards to the effectiveness of the screening programme should be conducted and this should involve a national register for Lynch Syndrome.

References

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., et al. 2011. Cancer risks associated with germline mutations in MLH1, MLH2 & MLH6 genes in Lynch Syndrome. *JAMA.* 305:22, 2304-2310.

Drummond, M.F., Sculpher M.J., Torrance, W.G., Brien, J.B., Stoddard. G.L. 2005. *Methods for the Economic Evaluation of the Health Care Programmes.* New York: Oxford University Press.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. 2009. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine.* 1: 1, 35-41.

Giardiello, F.M., Allen, J.I., Axilbund, J.E., Boland, R., Burke, C.A., 4 , Burt, RW., Church, JM., Dominitz, J.A., Johnson, D.A., Kaltenbach, T., Levin, T.R., Lieberman, D.A., Robertson, D.J., Sapna Syngal, S., Rex, DK. 2014. Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US. Multi-Society Task Force on Colorectal Cancer. *The American Journal of Gastroenterology.* 147, 502-526.

Palomaki, G.E., McClain M.R., Melillo, S., Hampel, H.L., Thibodeau, SN. 2009. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genetics in Medicine.* 11:1, 42-65.

Snowsill, T., Huxley, N., Hoyle, M., Jones-Hughes, T., Coelho, H., Cooper, C., Fraylin, I., Hyde, C., 2014. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. *Health Technology Assessment.* 18, 58.

Vasen, H.F.A., Blanco,I., Aktan-Collan, K., Gopie, J.P., Alonso, A., Aretz, S., Bernstein, I. (Mallorcca group). 2013. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut,* 62, 812–823.