Kent David Pluke

Lessons from a pilot study of screening for upper tract urothelial cell carcinoma in Lynch Syndrome

(HREC ref: 483/2018)

University Of Cape Town

Master of Medicine in Urology.

Table of contents

Declaration

The work contained in this document is based on independent work performed by myself, Kent David Pluke. None of this work is or has been submitted for another degree. The results of this research and conclusions made is authentic and original and has never been reported or published previously

Signed by candidate

29 July 2021

Abstract

HREC reference: 483/2018

Lessons from a pilot study of screening for upper tract urothelial cell carcinoma in Lynch Syndrome

Background: Lynch syndrome is a hereditary disorder, with a very high risk of the developing colorectal cancer (CRC) and a predilection to develop other cancers, including upper tract urothelial carcinoma (UTUC) that has an estimated lifetime risk of 0.2-25%, above that of the general population. Our aim was to assess the prevalence of UTUC in a Lynch syndrome cohort undergoing screening for CRC, to determine the need for a UTUC screening program.

Methodology: Lynch syndrome patients were screened with urine dipstix for microscopic haematuria. Patients with confirmed microhaematuria were offered urine cytology, microscopy and culture, ultrasound (US) of their upper tracts and flexible cystoscopy.

Results: Of the 89 patients screened, 86 had an MLH1 mutation and 2 had an MSH2 mutation. Eleven of the 12 patients who had microscopic haematuria were female. 10 patients had urinary tract infections. One patient had follicular cystitis and another had a simple renal cyst. No patients had hydronephrosis on ultrasound. All urine cytology specimens were negative for malignancy.

Conclusion: No cases of UTUC were detected in our cohort during this study. A more rational screening protocol in this group may be to screen patients for UTUC with known MSH2 mutations at an earlier age (over 35).

Keywords: upper tract urothelial cell carcinoma, integrated screening, existing colorectal malignancy screening program, Lynch syndrome

Acknowledgements and contributions.

I would like to acknowledge the following individuals for their selfless contribution to this project.

Dr Lisa Kaestner: Supervisor. Thank you for your patience and assistance. This project would not have materialized without your continuous support and motivation.

Professor Paul Goldberg: For your dedication to the patients with Lynch Syndrome. For allowing and making it possible to join the outreach team.

Sister Ursula Algar: Genetics sister and arranger of everything! Thank you for assisting me with everything I asked for and needed. From boxes to microscope to stickers to the genetics results! Your selfless dedication to the entire West Coast outreach project is exemplary and truly inspiring.

Dr Nkanyezi Sigasa: Thank you for assisting in the data collection.

Illustrations and tables:

	n	%		n	%
Sex			**Smoking history**		
Male	56	63	Smoker	46	52
Female	33	37	Non-smoker	43	48
Cancer			**Urinalysis**		
None	43		Haematuria	12	14
Colon	42	47	Leukocytes	77	86
Breast	1	1	Proteinuria	81	91
Endometrial	1	1	Nitrites	1	1
Duodenal	1	1	**Cytology**		
Multiple*	1	1	Negative	14	100
Total number of cancers	46	51	Positive	0	0
Genetic mutation			**Histology**		
MLH-1	86	98	No malignancy	4	100
MSH-2	2	2	Malignancy	0	0
USS findings			**Cystoscopy findings**		
Renal mass	0	0	Normal	9	56
Hydronephrosis	0	0	Cystitis	4	25
Bladder mass	0	0	Polyp	3	19

Table 1: Basic frequency table of data variables collected

	No cancer	Cancer	Total
Male	8	25	33
Female	35	21	56
Total	43	45	89

Table 2: 2x2 contingency table for gender and history of cancer.

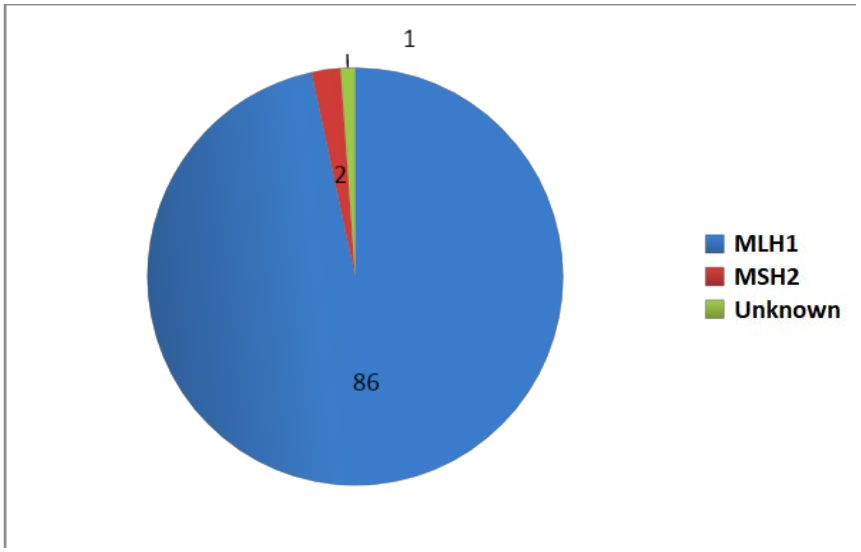

Figure 1: Gene mutation distribution

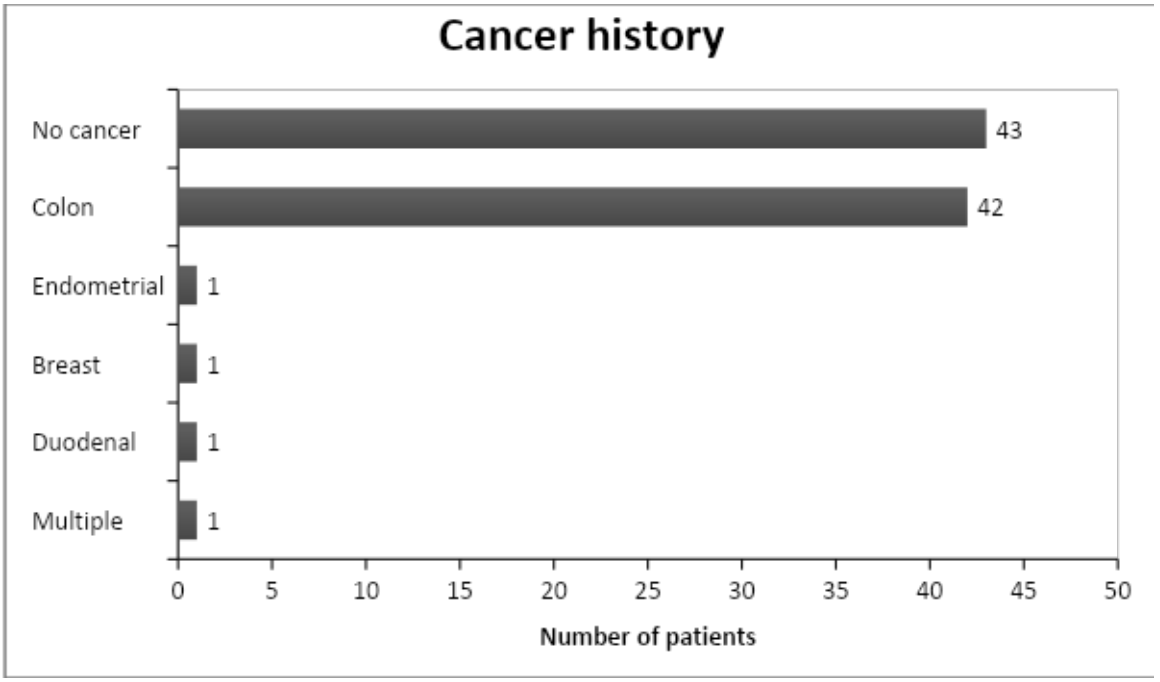

Figure 2: Bar graph depicting cancer history by anatomical location

Abbreviations

AUA: American Urological Association

CTU: Computed Tomography Urography

HNPCC: Hereditary non-polyposis colon cancer

KUB: Kidney, ureters and bladder

LS: Lynch Syndrome

MMR: Mismatch repair gene

UC: Urothelial carcinoma

UCT: University of Cape Town

US: ultrasound

UTI: urinary tract infection

UTUC: Upper tract urothelial carcinoma

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UROLOGY

Lessons from a pilot study of screening for upper tract urothelial cell carcinoma in Lynch syndrome

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Background: Lynch syndrome is a hereditary disorder, with a very high risk of developing colorectal carcinoma (CRC) and a predilection to develop other cancers, including upper tract urothelial carcinoma (UTUC). We aimed to assess the prevalence of UTUC in a Lynch syndrome cohort undergoing screening for CRC, to determine the need for a UTUC screening programme.
Methods: Lynch syndrome patients were screened with urine dipstick for microscopic haematuria. Patients with confirmed microhaematuria were offered urine cytology, microscopy and culture, ultrasound (US) of their upper tracts and flexible cystoscopy.
Results: Of the 89 patients screened, 86 had an MLH1 mutation and two had an MSH2 mutation. Eleven of the 12 patients who had microscopic haematuria were female. Ten patients had urinary tract infections. One patient had follicular cystitis and another had a simple renal cyst. No patients had hydronephrosis on ultrasound. All urine cytology specimens were negative for malignancy.
Conclusion: No cases of UTUC were detected in our cohort during this study. A more rational screening protocol in this group may be to screen patients for UTUC with known MSH2 mutations at an earlier age (over 35).
Keywords: upper tract urothelial cell carcinoma, integrated screening, existing colorectal malignancy screening programme, Lynch syndrome

Introduction

According to the American Urological Association (AUA), upper tract urothelial carcinoma (UTUC) is uncommon and accounts for only 5–10% of all urothelial cancers (UCs), with bladder cancer accounting for the remainder. UTUC has an estimated annual incidence in Western countries of ~2 cases per 100 000 inhabitants, with pyelocaliceal tumours about twice as common as ureteral tumours.[1] One of the risk factors identified for the development of UTUC is Lynch syndrome (LS). Individuals with LS have an estimated lifetime risk of developing UTUC of 0.2–25%, putting these individuals at a much higher risk than the general population.[2]

Lynch syndrome (also commonly referred to as hereditary non-polyposis colorectal cancer or HNPCC) is a hereditary autosomal dominant disorder, in which affected individuals have a much higher risk of developing certain cancers, with colorectal cancers being the most common. Other cancers include stomach, liver, gallbladder, upper urinary tract, ovaries, uterus, brain and skin. In LS, there is an inherited mutation in the gene coding for one of the following mismatch repair (MMR) genes: *MLH1, MSH2, MSH6* or *PMS2*. Currently, there is an LS registry in the Western Cape. Immunohistochemistry staining of resected colon cancers or polyp tissue is used to identify MMR deficiency. These patients and first-degree relatives are offered germline genetic testing for LS and are added to the registry if they are found to have a confirmed genetic mutation. This at-risk cohort is then entered into an active surveillance programme for colorectal cancer.[3]

Currently, there is no consensus on the appropriate screening tool for UTUC in LS patients, and if, in fact, a screening programme is needed in these patients. Scant literature is available on optimal screening for UTUC in LS and guidelines differ. The National Comprehensive Cancer Network advises annual urinalysis for haematuria from the age of 25–30 as a screening tool.[4] Current options cited by the Mallorca group for screening include annual urinalysis, urine cytology, ultrasound and cystoscopy. In view of the lack of evidence for the benefit of surveillance for urinary tract cancer, the Mallorca group does not recommend surveillance for urinary tract cancer in LS outside the setting of a research project.[5]

Patients with LS in South Africa are surveyed annually for colorectal malignancies and endometrial cancer. Little is known about their risk or history for UTUCs, and whether or not such screening is necessary. The aim of this pilot study was to assess the yield of haematuria in detecting UTUC or its precursors in the various gene mutations in an LS cohort in order to formulate screening recommendations for this population.

Methods

This pilot study enrolled patients from the Western Cape LS registry who attended ad hoc screening clinics in three local

town clinics along the north western coast of South Africa (Upington, Garies, and Vredenburg). Data and sample collection took place over the course of five days from those patients who gave informed consent.

Basic demographic data along with relevant past and present medical history, occupational history of employment in rubber, dye or chemical industries and smoking habits were recorded. The presence of haematuria was assessed by urine dipstick (CliniHealth Combi-10) and confirmed with microscopy done by the primary investigator. Participants with confirmed haematuria on microscopy had urine sent to the Groote Schuur Hospital National Health Laboratory Services (NHLS) laboratory for cytological analysis. KUB ultrasound and flexible cystoscopy were performed under local anaesthetic. Areas of abnormal bladder mucosa seen on cystoscopy were biopsied and the results were followed up three weeks after collection. MMR mutation status was recorded from the existing genetics database.

Statistical analysis was done using SPSS, with chi-squared t-tests for comparisons and statistical significance (p-value < 0.05).

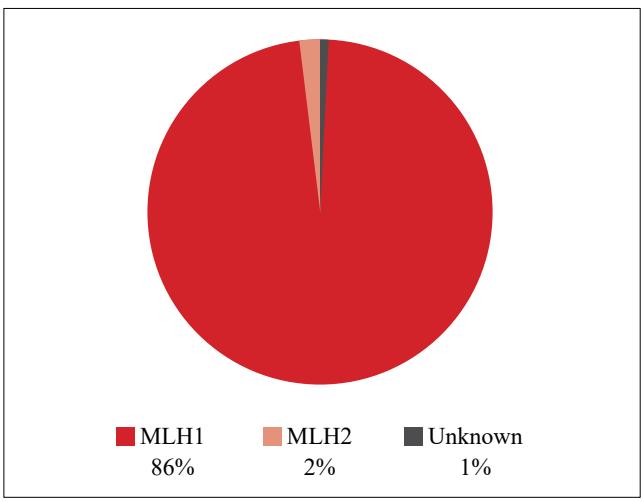
Informed verbal and written consent were obtained from all patients by the primary investigator.

Results

Eighty-nine patients met the inclusion criteria. There were 33 males and 56 females screened. The mean age of the patient cohort was 46 years (SD ± 10.86). In our cohort, 86 patients (98%) carried the MLH1 mutation, two patients were MSH2 carriers (Figure 1).

Forty-six (52%) patients had previous cancers (Figure 2). None of the patients in our study had a history of UTUC and there was no family history of UTUC reported. Smoking was not a statistically significant risk factor for developing colon cancer (risk ratio 0.78, $p = 0.33$). No patients had a history of occupational exposure to known risk factors for the development of TCC.

Twelve patients (14%) had microscopic haematuria on their urine dipstick and only one of them was male. A further four patients were found to have haematuria seen on microscopy only. Of the 16 patients who underwent cystoscopy, 56% were normal. Four patients (all females) showed features of cystitis (erythematous patchy mucosa or glandular epithelium). Single polyps were seen in three patients. There were no malignant cells reported in any of the cytology specimens. All bladder biopsy results were negative for malignancy. All patients who had an ultrasound of the bladder and kidneys were reported as normal (Table I).



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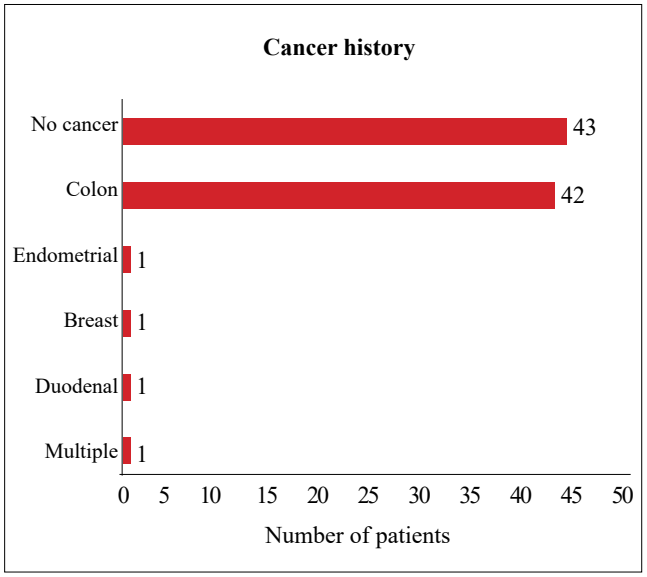

Figure 2: Bar graph depicting cancer history by anatomical location

Two patients were identified with MSH2 mutation and both had been diagnosed with previous colon cancer. 48% of patients with MLH1 mutation had a history of previous colon cancer (risk ratio 2.075; 95% CI 1.66–2.55).

Whilst not a primary objective of the study, an association was seen between gender and a diagnosis of previous colon cancer in our cohort. Gender was found to be a significant risk factor for the development of colon cancer. 25/33 (75%) of the males had a history of previous cancer vs only 21/56 (38%) for females (risk ratio 2,02; $p = 0.001$) (Table II).

Discussion

This is the first attempt to screen for UTUC in this LS population group in South Africa, who have a predominant unique mutation. In our cohort of patients, we did not find any evidence of UTUC. There were also no reports of any family members having UTUC. There are a number of possible reasons for this. UTUC is a rare cancer, and even though patients with LS are at increased risk, the chances of finding a patient with UTUC in a relatively small cohort are still quite low. The average age of patients in our study was 46, which is well below the age at which most patients with LS are diagnosed with UTUC. Rouprêt et al. report an average age at diagnosis of 60.[6]

There is currently no universally accepted screening protocol for patients with LS, although a recent consensus by a panel of UTUC experts advised annual urinalysis for haematuria. Patients found to have micro-haematuria should be investigated further with urine cytology and KUB ultrasound or computerised tomography urography (CTU). Cystoscopy was shown to have a poor pick-up rate unless combined with retrograde studies of the ureters.[7] Retrograde ureterorenoscopy is a poor screening investigation because it is expensive, and increases UTI and ureteric injury risk. Although unlikely, it is possible that current screening methods are missing very early UTUCs.

Table 1: Basic frequency table of data variables collected					
	n	%		*n*	%
Sex			**Smoking history**		
Male	56	37	Smoker	46	52
Female	33	63	Non-smoker	43	48
Cancer			**Urinalysis**		
None	43		Haematuria	12	14
Colon	42	47	Leukocytes	77	86
Breast	1	1	Proteinuria	81	91
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Table 2: 2x2 contingency table for gender and history of cancer			
	No cancer	**Cancer**	**Total**
Male	8	25	33
Female	35	21	56
Total	43	45	89

There is growing evidence that certain subsets of patients with LS are at much greater risk of developing UTUC at a younger age. Evidence suggests that carriers of MSH2 mutation and MSH6 combined with MSH2 mutation are at much higher risk of developing UTUC than LS patients with MLH1, with a lifetime risk of between 5% and 11.3%.[8-11] In fact, there is very little evidence that links MLH1 carriers with an increased risk of UTUC. Some authors suggest only screening patients with MSH2 mutation for UTUC.[12] 98% of our patient cohort had MSH1 mutations, with only two patients being affected by MSH2 mutation. Both MSH2 carriers died within months following our study. The ages of the patients were 47 and 54 years old. The cause of death was not available to us, but it does raise the question whether these patients died of extra-colonic malignancies, as they had recently been screened negative for colon cancer.

In our cohort of predominantly MLH1 mutations, male gender increased the relative risk of developing colon cancer by twofold. This result was statistically significant ($p = 0.001$). This trend was also noted in a large, observational, international, multicentre study aimed to determine prospectively observed incidences of cancers and survival in *MMR* carriers up to 75 years of age.[13] The reason for this observation in MLH1 mutation carriers specifically is currently unclear.

A key limitation to our study is the cross-sectional design. Our study provided a 'snapshot' prevalence, whereas a long-term prospective study may provide a more accurate indication of the true incidence rate of UTUC in this cohort. Another limitation is the diagnostic tools used to screen for UTUC. The most accurate investigations for the diagnosis of UTUC are CTU or retrograde pyelogram and ureteroscopy, but these are not practical screening investigations as they are expensive and invasive.

Conclusion

Our study identified no cases of UTUC despite an extensive screening protocol. This is likely explained by the fact that the majority of LS patients in our study population have MLH1 mutation. This further bolsters evidence that these patients do not seem to have a significantly increased risk of developing UTUC compared to the general population. A more rational screening protocol may be to only screen patients with MSH2 mutations for UTUC at an early age. Ideally, a longer-term follow-up in a bigger cohort would yield more valuable results, but this pilot study, with its obvious limitations, failed to show evidence for significant benefit of a formal screening programme for UTUC in this patient cohort.

Acknowledgements

We would like to thank the following individuals: Professor Paul Goldberg and the colorectal unit at Groote Schuur Hospital, Sister Ursula Algar and Dr Nkanyezi Sigasa.

Conflict of interest

The authors declare no conflict of interest.

Funding source

None.

Ethical approval

Ethical approval was obtained from University of Cape Town Human Research Ethics Council (UCT HREC) before any data collection took place. (HREC reference 483/2018).

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Appendices

Questionnaire/data capture instrument

	yes	no
Patient demographics		
● Age (in years)	●	●
● Gender	● male	● female
Risk factors		
● Previous Cancers ● If yes, type of cancer	●	●
● Smoking history	●	●
● Occupation	●	●
● Family history of UTUC	●	●
● Results of prior genetic testing if available	●	●
Urinalysis results		
● Haematuria	●	●
● Proteinuria	●	●
● Leukos	●	●
● Nitrites	●	●
Ultrasound report (if done)		
● Renal mass?	●	●
● Hydronephrosis?	●	●
● Bladder mass/mucosal thickening?	●	●
Cytology results (if done)		
Cystoscopy report (if done)		

Information regarding results of further workup and management for UTTCC at Groote Schuur Hospital.	

Consent forms and participant information sheet:

Information sheet and informed consent for research study:

Integrating screening for upper tract urothelial cell carcinoma into an existing colo-rectal malignancy screening program in a Western Cape population with Lynch Syndrome

PURPOSE OF THE STUDY

We are conducting a study to determine if there is an increased risk for patients with Lynch Syndrome to develop cancer in the kidney or ureters, a tube connecting the kidneys to the bladder. The benefit of this would be to potentially find and treat these cancers early in their disease course.

We require your participation in the study to use the information to make decisions on how to best monitor and detect cancers of the ureter, bladder and kidney early. This information could directly benefit you and many others with Lynch syndrome in future.

PARTICIPANT SELECTION

We are inviting all patients over the age of 30 who have been identified as having the Lynch syndrome gene to participate in this study.

PARTICIPANT INVOLVEMENT

If you agree to partake in the study, you will be asked to provide a urine sample which will be tested. You will then be asked a few short questions. If traces of blood are found in your urine sample you will be offered an ultrasound scan of your kidneys and bladder as well as cystoscopy. A cystoscopy is a short (two to five minutes), painless procedure in which a tiny flexible camera is inserted into your bladder through your urethra. The urethra is the tube or ‘pipe’ that allows the passage of urine from your bladder to the outside. Cystoscopy carries a very small risk of developing infection in the bladder and kidneys, participants who require one will be given an antibiotic before the procedure. If you require this procedure the doctor will provide you with more detailed information about the procedure before asking your written consent

The questionnaire will take approximately five minutes of your time. If you undergo an ultrasound and cystoscopy, this will require approximately an extra thirty minutes of your time.

A flexible cystoscopy is a procedure during which a small, flexible camera is inserted into the bladder via the patient's urethra. It is generally painless and done within two to three minutes. Adults do not require sedation or analgesia for this procedure. If the doctor observes a suspicious lesion, he or she may opt to take a small sample (this is known as a biopsy). The biopsy may cause brief discomfort and some patients may observe slightly blood-stained urine for a day or two thereafter. Less than one percent of patients may develop a urinary tract infection after a cystoscopy, which will require antibiotic treatment.

What if Something Goes Wrong?

The University of Cape Town (UCT) undertakes that in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity, that is caused by your participation in the study, it will provide immediate medical care. UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly-speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

PAYMENT/COMPENSATION FOR PARTICIPATION

Participation is completely voluntary and you may opt out at any time. Refusing or withdrawing from the study will not affect your treatment in this clinic in any way. There will be no compensation for participation this study.

FOLLOW UP OF PARTICIPANTS

If during the study, it is picked up that you have a possible cancer or any other pathology, the investigating doctor will discuss the findings with you and arrange for care either at your local hospital (if they are able to assist you), or at Groote Schuur Hospital department of Urology in Cape Town. This will be at no extra cost to you.

USE OF MEDICAL INFORMATION

Please take note that by agreeing to participate in this study you agree to the use of all your medical information collected FOR THE PURPOSE OF THIS STUDY ONLY

CONFIDENTIALITY

Your personal information will not be shared with any third parties. Any identifiable information obtained in connection with this study will remain confidential and will be stored on a password protected computer until after the study has been completed and then destroyed.

INVESTIGATOR CONTACT INFORMATION

Investigator: Dr Kent Pluke via e-mail at plkken001@gmail.com or via telephone at 0214046105.

UCT HUMAN RESEARCH ETHICS COMMITTEE: shuretta.thomas@uct.ac.za Tel 021 406 6626

CONSENT

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

RESEARCHER STATEMENT

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Urine dipstix test

2. medical information/data sheet

3. possible ultrasound and cystoscopy

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my

ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____ (Day/month/year)

• Official Ethics approval letter from the Faculty Research Ethics Committee

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682
Email: suraya.basterman@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 June 2019

HREC REF: 483/2018

Dr L Kaestner
Division of Urology
E26
NGSH

Dear Dr Kaestner

PROJECT TITLE: INTEGRATING SCREENING FOR UPPER TRACT UROTHELIAL CELL CARCINOMA INTO AN EXISTING COLO-RECTAL MALIGNANCY SCREENING PROGRAM IN A WESTERN CAPE POPULATION WITH LYNCH SYNDROME (MMED CANDIDATE: Dr K PLUKE)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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 30 June 2020.

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)

Please quote the HREC REF number in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that Dr Kent Pluke will be involved in this study.

Yours sincerely

pp TBurgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.