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Non-invasive diagnosis of urinary bladder cancer

Submission date 02/09/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 04/09/2020	**Overall study status** Completed	
Last Edited 04/05/2023	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Urothelial cancer (cancer in the bladder, ureter or renal pelvis) is amongst the most common malignancies in the world. The disease mainly affects the elderly, while it is uncommon among those younger than 50 years of age, with a median age of 73 years at diagnosis. About three quarters of patients diagnosed with urothelial cancer (UC) are men.

The most common symptom of UC is macroscopic haematuria (visible blood in the urine). According to clinical guidelines, macroscopic haematuria should be investigated with cystoscopy and computed tomography with urographic imaging (CT urography) of the upper urinary tract (ureter and renal pelvis). In Sweden, a standardised care pathway has been in effect since 2015 which mandates this investigation for all patients older than 50 years of age with macroscopic haematuria, and which should be completed within one week. More than 90 % of UC is located in the bladder (bladder cancer), with about 2500 new cases in Sweden annually, most of which are diagnosed with cystoscopy.

Among patients investigated in such a standardised care pathway, 8-10 % are diagnosed with UC. Both cystoscopy and radiologic imaging of all patients with macroscopic haematuria are very resource-intensive, leading to delays completing the investigations beyond the mandated week. In addition, cystoscopy is an invasive procedure with significant discomfort, and which leads to infections in up to 5 % of patients. It is therefore desirable to develop a non-invasive assay to better select patients for whom cystoscopy can be avoided, and thus be able to concentrate resources on the patients who are more likely to need timely investigations.

Non-invasive tests have been studied previously. The first was urine cytology, which shown however to have a high variability between those assessing the results and low sensitivity, especially for low-grade tumours. UroVysion was developed as an adjunct to cytology and is a fluorescence in-situ hybridisation (FISH) analysis of urine cytology, which detects specific genetic amplifications in urothelial cells. However the sensitivity of this test is still too low to be used to exclude further investigations, and it still suffers from a high variability.

Recently, newer mRNA and epigenetic-based assays have been reported and made commercially available. Xpert Bladder Cancer Detection is an assay based on levels of specific mRNA in urine,

which are elevated in UC. It has reported a very high sensitivity, but only where data has been assessed retrospectively after a diagnosis of UC. The result is given as a risk of cancer so that the threshold for further action can be modified depending on the clinical setting.

CT urography, which is the clinical standard used to detect urothelial cancer in the upper urinary tract, can also visualise urinary bladder cancer. It has previously been shown that by timing the contrast phases appropriately, bladder cancer can be detected with high sensitivity without performing more series or using a higher radiation dose. This protocol is therefore currently in clinical use at most centres. However, the results have not been validated outside the initial investigation centre.

The aims of this project are therefore to evaluate the Xpert Bladder Cancer Detection test and CT urography, separately and combined, in a prospective study of patients investigated in a standardised care pathway.

Who can participate?
All patients referred for evaluation of macroscopic haematuria according to the standardised care pathway at participating centres will be offered participation.

What does the study involve?
Prior to cystoscopy participants will give a urine sample and fill out a questionnaire regarding their symptoms. Participants will undergo cystoscopy (A thin camera inserted into the urethra) and CT urography (a scan of the pelvis). Participants with signs of, or suspected signs of, urothelial cancer from these tests will have the urine sample analysed with GeneXpert Bladder Cancer Detection. Subjects with negative findings of urothelial cancer will be randomised for analysis or not. The outcome of investigations for urothelial malignancy up to one year after enrolment will be collected retrospectively from medical records.

What are the possible benefits and risks of participating?
The participants and clinical physicians will be blinded to the results of the urine analysis, so participants will not themselves have any benefits, but are also there are no physical risks associated with participation.

Where is the study run from?
The Department of Urology, Sahlgrenska University Hospital (Sweden), in collaboration with the Department of Surgery, NU-sjukvården (Sweden)

Then is the study starting and how long is it expected to run for?
From September 2019 to January 2024

Who is funding the study?
Grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG-873181), and from the Swedish Society of Medicine (SLS-890771)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
Non-invasive diagnosis of urothelial carcinoma with urinary biomarkers and imaging after macroscopic haematuria

Study objectives
Urine analysis using GeneXpert Bladder Cancer Detection and/or CT urography can be used to select patients with macroscopic haematuria, for whom the risk of underlying urothelial malignancy is so low that cystoscopy is not needed.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/12/2019, Swedish Ethical Review Authority (Box 2110, 750 02 Uppsala; +46 10-4750800; registrator@etikprovning.se), ref: 2019-05582

Study design
Prospective observational case-control single-centre study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Only available for patients at participating centres

Health condition(s) or problem(s) studied
Diagnostic workup in patients with macroscopic haematuria

Interventions
Patients undergoing diagnostic workup according to a standardised care pathway for macroscopic haematuria will leave urine sample prior to cystoscopy. For the participants where cystoscopy detects a suspected urinary bladder cancer (expected 8% of all included participants) and a random sample of 1 in 15 with normal cystoscopy, GeneXpert Bladder Cancer Detection analysis will be performed. All participants will also undergo a computed tomography urography, including an image sequence with contrast in late arterial phase, according to the standardised care pathway.

Intervention Type
Other

Primary outcome measure
Diagnosis of urinary bladder cancer within one year of enrolment collected retrospectively from medical records at 1 year after enrolment

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
01/08/2019

Completion date
01/01/2024

Eligibility

Key inclusion criteria

1. Aged ≥50 years
2. Referred to participating centres for evaluation of macroscopic haematuria according to standardised care pathway
3. Able to give signed informed consent

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
2000

Total final enrolment
1516

Key exclusion criteria
1. History of urothelial carcinoma
2. Unable to give voided urine sample/has urine catheter

Date of first enrolment
09/09/2020

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
Sweden

Study participating centre
Kirurgmottagning Uddevalla Sjukhus
Fjällvägen 9
Uddevalla
Sweden
45180

Sponsor information

Organisation
Västra Götaland Regional Council

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Sponsor type
Government

Website
https://www.vgregion.se

ROR
https://ror.org/00a4x6777

Funder(s)

Funder type
Government

Funder Name
Svenska Läkaresällskapet

Alternative Name(s)
Swedish Society of Medicine, Swedish Medical Society, SLS

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Sweden

Funder Name
ALF-agreement: Swedish state under the agreement between the Swedish government and the county councils

Results and Publications

Publication and dissemination plan
Planned publication in peer-reviewed journal

Intention to publish date
01/09/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Henrik Kjölhede, henrik.kjolhede@vgregion.se, on publication of results and for 10 years, for research purposes by researchers in public institutions within the European Union, in anonymised form.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		04/09/2020	08/09/2020	No	No