Summary
Bladder cancer is the 10th most common cancer type worldwide and is one of the most challenging and expensive cancers to diagnose and treat. Its diagnosis relies on cystoscopy, an invasive and expensive procedure that might not be easily accessible in low-resource settings. IARC has developed a urine assay that detects mutations in the promoter of the \textit{TERT} gene (\textit{uTERTpm}) and has shown its excellent performance for the detection of bladder cancer in urine samples in two independent studies. The detection of this biomarker is simple and non-invasive and could provide a cost-effective tool to improve both early detection of bladder cancer and monitoring of recurrence. It may also open new avenues for screening of high-risk populations (smokers and workers exposed to bladder carcinogens).

Introduction
Every year, about 600,000 people are diagnosed with bladder cancer worldwide and more than 200,000 people die from this disease. The rates of newly diagnosed bladder cancer are highest in Western and Southern Europe, North America, and Northern Africa. Although men are 3 times as likely as women to develop bladder cancer, women are typically diagnosed with more advanced cancer and have a worse prognosis than men. Risk of bladder cancer increases with age: about 90% of cases are diagnosed in people older than 55 years, and 50% in those older than 70 years.

Most bladder cancers are diagnosed at an early stage (75% are diagnosed as non-muscle-invasive carcinoma), when they are highly treatable. However, even early-stage bladder cancer can recur after successful treatment (31–78% recurrence at 5 years). Therefore, people with bladder cancer typically need to be followed up closely for years after treatment, which may also include performing invasive procedures such as cystoscopy. About 25% of bladder cancers are diagnosed at later stages. For the most advanced stages, the percentage of people surviving 5 years after diagnosis is only 6%. These survival rates have not improved during the past 30 years.

The main sign of bladder cancer is blood in the urine (called haematuria). Other signs include frequent urination or pain when urinating and abdominal, lower back, or pelvic pain. Bladder cancer is diagnosed mainly through an invasive and expensive procedure called cystoscopy. In this procedure, a urologist uses a cystoscope – a long, thin, flexible tube with a light and a lens or a small video camera – to see inside the bladder.

Therefore, early diagnosis and improved monitoring would greatly contribute to reducing bladder cancer mortality, decreasing the associated economic burden, and improving the patients’ quality of life.
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Key evidence messages
- There is a tremendous need for a robust, cost-effective, and non-invasive method for early detection of bladder cancer, to complement or replace the diagnostic standard of invasive cystoscopy.
- To be clinically useful, the method should:
  - be sensitive, specific, and robust;
  - demonstrate improved diagnostic accuracy compared with cystoscopy;
  - demonstrate improved health outcomes compared with current practice;
  - be easily implementable into routine clinical practice; and
  - be cost-effective (see Figure 1).
- The detection of urinary TERT promoter mutations (uTERTpm) is a simple and non-invasive method.
- uTERTpm testing, followed by cystoscopy or urography, could provide a cost-effective tool for screening of high-risk populations (smokers and workers exposed to bladder carcinogens).
- This research-based evidence needs to be translated into clinical practice to improve the management of patients with bladder cancer and high-risk populations.
- The health benefits of a promising urinary biomarker such as uTERTpm include:
  - improved detection of early-stage bladder tumours or early recurrence, which could lead to better survival;
  - reduced numbers of unnecessary invasive cystoscopy procedures in patients with a negative uTERTpm test result;
  - increased adherence of high-risk populations to a simple, harmless screening programme; and
  - reduced cost of clinical management of suspected bladder cancer (i.e. €25 per uTERTpm biomarker test).
- Including patient perspectives in research will make scientific and medical advances more timely and effective for people with bladder cancer.

Barriers to early diagnosis, and existing bladder cancer biomarkers
Currently, detection of bladder cancer relies mainly on cystoscopy, which is an invasive and expensive procedure that might not be easily accessible in low-resource settings. Some imaging studies and non-invasive tests, such as urine cytology or urine biomarkers, have also been proposed as complementary diagnostic modalities, but none of them have shown optimal performance to be used for early detection of bladder cancer (i.e. lack of sensitivity and/or specificity and/or cost–effectiveness). For instance, none of the commercially available urine biomarkers approved by the United States Food and Drug Administration (FDA) are recommended by urological societies for routine clinical management of bladder cancer or screening in high-risk populations. Thus, invasive cystoscopy, often combined with urine cytology, remains the diagnostic standard in many practices.

Another barrier to early diagnosis of bladder cancer is the delay between referral to a clinician and diagnosis. Regular non-invasive screening of asymptomatic high-risk populations would reduce the delay in bladder cancer diagnosis.

Call to action

The research community should validate the uTERTpm droplet digital PCR (ddPCR) assay for the detection of bladder cancer in urine.

The research community should evaluate the effectiveness of uTERTpm for screening strategies in high-risk populations.

Public and private funders should invest in research to fully assess the robustness of uTERTpm as a universal biomarker for early detection and monitoring of bladder cancer.

Urological societies should adopt research-based evidence to integrate uTERTpm into routine clinical management of bladder cancer and screening programmes.
Urinary TERT promoter mutations (uTERTpm) as a non-invasive biomarker for the early detection of bladder cancer

IARC has led studies to evaluate a urine test for the early detection of bladder cancer. This test detects the presence of specific mutations in the promoter of the telomerase reverse transcriptase (TERT) gene in urine samples. These TERT promoter mutations (TERTpm) have been detected at a high frequency (60–85%) in all stages and grades of bladder cancers and are the most frequent genetic alterations. IARC has developed a droplet digital PCR (ddPCR) assay to detect TERTpm in urine samples. This assay (uTERTpm) is easily implementable into routine clinical practice.

This assay was tested in two studies: the DIAGURO study in France and the Golestan Cohort Study in the Islamic Republic of Iran. It showed excellent performance for the detection of bladder cancer in urine samples. The uTERTpm marker was detected in the urine of most patients with bladder cancer (up to 87%) at the time of diagnosis, whereas it was detected in the urine of only 5% of the participants who did not have bladder cancer at the time of urine collection. The uTERTpm biomarker was also detected in the urine of asymptomatic individuals up to 10 years before the clinical diagnosis of bladder cancer.

Could uTERTpm be a screening tool in high-risk populations?

Although bladder cancer screening is currently not recommended by the clinical guidelines or urological societies, probably because none of the commercially available urine tests have shown appropriate performance for this purpose, screening high-risk populations would enable improvement in bladder cancer survival, by reducing the stage at which the cancer is discovered.

Haematuria is the most common symptom of bladder cancer and the easiest to measure. However, microhaematuria (non-visible blood in urine) occurs in the urine of 2–30% of the general population, of whom only 1–5% will be diagnosed with bladder cancer. Therefore, it is important to adapt screening recommendations to identify high-risk populations that could benefit most from bladder cancer screening, and to help avoid unnecessary invasive procedures for low-risk populations.

Current procedures to detect bladder cancer, and their limitations

- Diagnostic standard:
  - Cystoscopy: invasive and expensive
- Complementary methods:
  - Imaging approaches such as computed tomography: expose the patient to X-rays, ionizing radiation
  - Urine cytology: lacks sensitivity for detecting low-grade tumours
  - FDA-approved urine biomarkers: lack performance and consistency; not cost-effective

Fig. 1 Road map of the urinary TERT promoter mutations (uTERTpm) biomarker for the early detection and monitoring of bladder cancer.

“uTERTpm could be the first urine marker to be used in routine bladder cancer clinical practice, but first it needs to be fully validated in large, well-designed international studies.”

– Dr Florence Le Calvez-Kelm

DIAGURO study in France

- 93 patients diagnosed with primary or recurrent bladder cancer (urothelial carcinoma) and 94 patients with urological conditions other than bladder cancer.
- The uTERTpm biomarker was assessed in urine samples with the UroMuTERT assay.
- 87% of patients with bladder cancer were positive for the marker.
- 95% of individuals without any sign of bladder cancer were negative for the marker (see Figure 2).

Golestan Cohort Study in the Islamic Republic of Iran

- 50,045 individuals aged 40–75 years, recruited in Golestan Province in north-eastern Islamic Republic of Iran in 2004–2008, gave a urine sample at the time of recruitment and were followed up for 14 years.
- uTERTpm was assessed in the urine of the 38 participants who developed primary bladder cancer (urothelial carcinoma) during the follow-up and 152 healthy individuals without any history of cancer at the end of follow-up.
- uTERTpm was assessed with a combination of two independent methods: the UroMuTERT and droplet digital PCR (ddPCR) assays.
- 46.7% of initially asymptomatic individuals who developed bladder cancer during the follow-up were positive for the marker.
- 100% of individuals without any sign of bladder cancer were negative for the marker.
- uTERTpm was detected in urine samples up to 10 years before the diagnosis of bladder cancer.
The uTERTpm biomarker offers a significant opportunity as a simple and non-invasive biomarker for screening and early detection, because it is detectable years before the clinical diagnosis of bladder cancer (see Figure 3). This idea is further supported by studies showing that screening high-risk populations using inexpensive and robust urinary biomarkers followed by cystoscopy could be cost-effective. Therefore, detection of TERTpm in urine may be considered as a promising candidate for cost-effective screening programmes targeting the appropriate high-risk populations. The utility of uTERTpm as a primary screening or early detection biomarker should be assessed in asymptomatic individuals who are at high risk of developing bladder cancer, including those who smoke cigarettes or are exposed to bladder carcinogens, and in individuals with haematuria.

Could uTERTpm be a biomarker for post-surgery monitoring?
Localized bladder cancers (non-muscle-invasive carcinomas) are removed through the urethra. However, because of the high recurrence rates associated with the disease, post-surgical follow-up requires many cystoscopies; the procedure is repeated every 3–6 months for 5 years for intermediate-risk patients and lifelong for high-risk patients. The utility of uTERTpm in follow-up urine samples requires further investigation. It could potentially reduce the number of unnecessary repeated – expensive and invasive – cystoscopies during long-term follow-up and provide an early urine biomarker of recurrence.

The socioeconomic burden of bladder cancer, and how uTERTpm could alleviate it
Currently, bladder cancer is one of the most challenging and expensive cancers to diagnose and treat, with large cost discrepancies between countries (e.g., expenditure per patient in the USA is twice that in the European Union). The largest components of the costs are inpatient care (including the various detection examinations; 59%) and medicines (20%). The cost contribution of repeated cystoscopies is significant (€250–600 each, depending on the country). It is an invasive examination and can cause a range of discomfort and complications, lowering patients’ quality of life and probably resulting in reduced adherence to surveillance protocols. Although urine cytology is less expensive (€25–100 each), it has poor sensitivity for detecting low-grade tumours and is used only as a complementary method.

The cost of uTERTpm biomarker testing would be about the same as that of a urine cytology test (i.e., €25) and about 4–10% that of cystoscopy. Therefore, this test could provide a cost-effective alternative to expensive and invasive examinations, without any side-effects.

“This urine test based on the detection of TERT promoter mutations (uTERTpm) could significantly improve the way bladder cancer is detected, which is still currently based on expensive and invasive methods.”

– Dr Arnaud Manel
Implications
The validation of uTERTpm as a urinary biomarker of bladder cancer in international studies would provide valuable information to aid its clinical implementation, possibly including the development of screening strategies in high-risk groups, who would benefit from close surveillance with a simple, non-invasive test.

Potential long-term public health and economic benefits of this biomarker include:

- improved detection of early-stage bladder cancer, leading to better survival;
- reduced numbers of unnecessary cystoscopy procedures in patients with a negative uTERTpm test result;
- improved surveillance for bladder cancer recurrence with dynamic monitoring of the marker, reducing the number of unnecessary repeated – expensive and invasive – cystoscopies during long-term follow-up;
- reduction of possible complications and discomfort associated with unnecessary invasive procedures, thus increasing the proportion of patients who adhere to screening or surveillance protocols; and
- reduction of costs related to the unnecessary clinical procedures.

In summary, the validation of uTERTpm as a simple, sensitive, and cost-effective urinary biomarker of bladder cancer could lead to a significant improvement in the early detection and management of bladder cancer, thus contributing to decrease the global burden of bladder cancer.

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