**Urine profiling as a source of biomarker in cancer detection: A review**

**Abstract:**

Urine is a compound that contains nitrogen-specific elements such as urea, uric acid, and creatinine. Historically, urine has been used to offer medically helpful insights into human health and illness, making it one of the earliest non-invasive diagnostic fluids. With advances in molecular biology, urine-based biomarker identification has shown potential in the detection of various cancers, including bladder, prostate, and hepatocellular carcinoma.

Urine cells contain DNA, RNA, circulating tumor DNA (ctDNA), and long non-coding RNA (lncRNA), all of which serve as possible biomarkers. This review focuses on urine biomarkers involved in bladder cancer, including DNA markers, RNA markers, protein markers, and metabolites. Analysis of urine in Non-Muscle Invasive (NMIBC) and Muscle Invasive (MIBC) bladder cancer types offers a promising diagnostic and systematic approach, particularly using Mass Spectrometry (MS) and Nuclear Magnetic Resonance (NMR)-based techniques.

Currently, FDA-approved molecular biomarkers such as BTA stat, BTA TRAK, and NMP22 are used to monitor bladder tumors. The Bladder Tumor Antigen (BTA) agglutination test identifies complement factor H-related protein in excreted urine. However, the sensitivity of BTA stat in tumor detection has been reported to vary between 40–70%, while specificities range from 29–96%. Despite these limitations, the discovery of novel potential biomarkers from urine is ongoing, with numerous studies continuing to explore their diagnostic potential.

In this review, we aim to identify and evaluate urine-based biomarkers across different cancer types—particularly bladder cancer—through the inclusion of recent research findings. We also seek to gain novel insights to standardize testing procedures and validate these biomarkers in a clinical setting. The implications of this research include easier detection, reduced invasiveness, and improved disease monitoring, ultimately paving the way for more accurate diagnosis, better treatment options, and enhanced patient outcomes in the near future.

**Keywords:** Biomarkers,BTA stat, BTA TRAK, NMP22, NMIV, MI, Urovisyon, Urinary liquid biopsy, etc.

1. **Introduction:**

Urine is a by-product of kidney metabolism. Many nitrogen-containing compounds, such as urea, uric acid, and creatinine, are ejected from the body during the process of urination. However, urine also includes a number of organic substances, including proteins, hormones, and metabolites, as well as inorganic salts. Nitrogen, ammonium, ammonia nitrogen, nitrate, nitrite, phosphorus, potassium, sulfate, sodium, magnesium, chloride, and calcium make up the majority of the chemical components of fresh urine [1-3]. Additionally, the color of healthy people's urine is clear or light yellow. Urine has been wildly used to offer medically helpful insights on people's health and illness [4]. The presence of unnatural color, smell or components may aid us to detect the disease condition of the respective individual by analyzing the urine. Likewise, presence of fruity odor of urine or acidic nature may indicate the ketosis or diabetic condition of the patients [5-6]. In addition to the disease diagnosis, analysis of urine plays a pivotal role in detecting cancer as well as designing treatment based on it. However, analysis of urine as a diagnostic tool was gold standardized by using several classical methods of microscopic technology and systematic analysis which has been evolved into NMR-based and mass spectrometry (MS)-based identification of metabolites [7-8].

However, urine has a crucial role in terms of Noninvasive Cancer diagnostics, It is involved in most of the cancer types. In Noninvasive cancer, urine can be easily collected without the medical professional. It can be collected without any restrictions and enabling serial collection and multi-omics analysis [9-10]. Several reports have been published on urine profiling as a diagnostic and prognostic biomarker for cancer detection [bladder, prostate, hepatocellular etc. [11]. This review seeks to focus on the profiling of urine components and its utility in oncology, mainly in bladder cancer, prostate cancer, hepatocellular carcinoma, renal cell carcinoma etc.

1. **Routine urine diagnosis:**

Routine urine diagnosis is known as urinalysis. It is a common clinical test to know general health and also helps in detection of various disorders like urinary tract infections, diabetes, kidney disease, etc. Urinalysis includes mainly three components: physical examination, chemical examination, and microscopic analysis. The physical examination is based on color, clarity, etc.; whereas chemical evaluation is based on pH, specific gravity, glucose, protein, nitrites, leukocyte esterase, etc.; and microscopic analysis focuses on cells, casts, crystals, microorganisms, etc. Collecting urine is easy, non-invasive, and inexpensive, that’s why it is often used in both routine checkups and initial diagnostic evaluations (12).

In oncology, routine urinalysis can help to detect early signs of urological malignancies by detection of hematuria, which may indicate bladder, renal, or prostate cancers. But, the specificity and sensitivity of urinalysis solely are limited, and such findings often refer further diagnostic imaging or molecular, cytological testing [12-13]. Though there are some limitations, urine can be used as a diagnostic medium due to its unique biochemical composition and the absence of strong homeostatic regulation, which allows it to reflect dynamic physiological and pathological changes more sensitively than blood [13].

Urine generally contains several biological molecules, including cell-free DNA, RNA, microRNAs, proteins, metabolites, and extracellular vesicles such as exosomes, all of which are being investigated as potential biomarkers for cancer detection and prognosis [14]. Of late, advancements in molecular diagnostics have significantly expanded the role of urine beyond traditional analysis. By combining with omics (such as proteomics, genomics, and metabolomics), routine urine diagnosis can be used as a powerful platform for non-invasive cancer diagnostics [14]. This makes it particularly attractive for early detection, patient stratification, and monitoring disease progression or therapeutic response, especially in resource-limited, cost-effective settings.

1. **Urine in Cancer and diagnosis:**

Urine is now widely used as an important biofluid in cancer diagnostics. Urine collection is non-invasive, easy and urine consists of stable molecular components, as well as diverse range of detectable biomarkers that are necessary for early detection of cancer. Unlike blood samples, urine is not under tight homeostatic control, which allows subtle biochemical changes associated with malignancy to be more easily identified [15]. Urine also contains wide range of cancer-related molecules, including cell-free DNA (cfDNA), microRNAs, proteins, metabolites, and exosomes, which can sign presence of tumor, type, and progression.

Traditionally, urine has been used to detect the urological cancers, specially bladder and kidney cancer, through cytology and/or dipstick tests which reveal hematuria. But these methods lack sensitivity, particularly for early-stage cancer [16]. Recently, molecular profiling of urine sample has come up as a promising approach for early detection and monitoring of cancer. For example, urinary PCA3 RNA is clinically approved biomarker for the diagnosis of prostate cancer, outperforming prostate-specific antigen (PSA) in specificity [15-16].

Researchers observed not only urologic malignancies, but also other cancers such as breast, lung, and colorectal can leave molecular signatures in urine, which can easily be detected through high-throughput omics approaches [15]. This broadens the scope of urine-based diagnostics in oncology and supports its role in non-invasive cancer screening, personalized treatment, and real-time disease monitoring.

1. **Significance of urine components for disease-detection:**

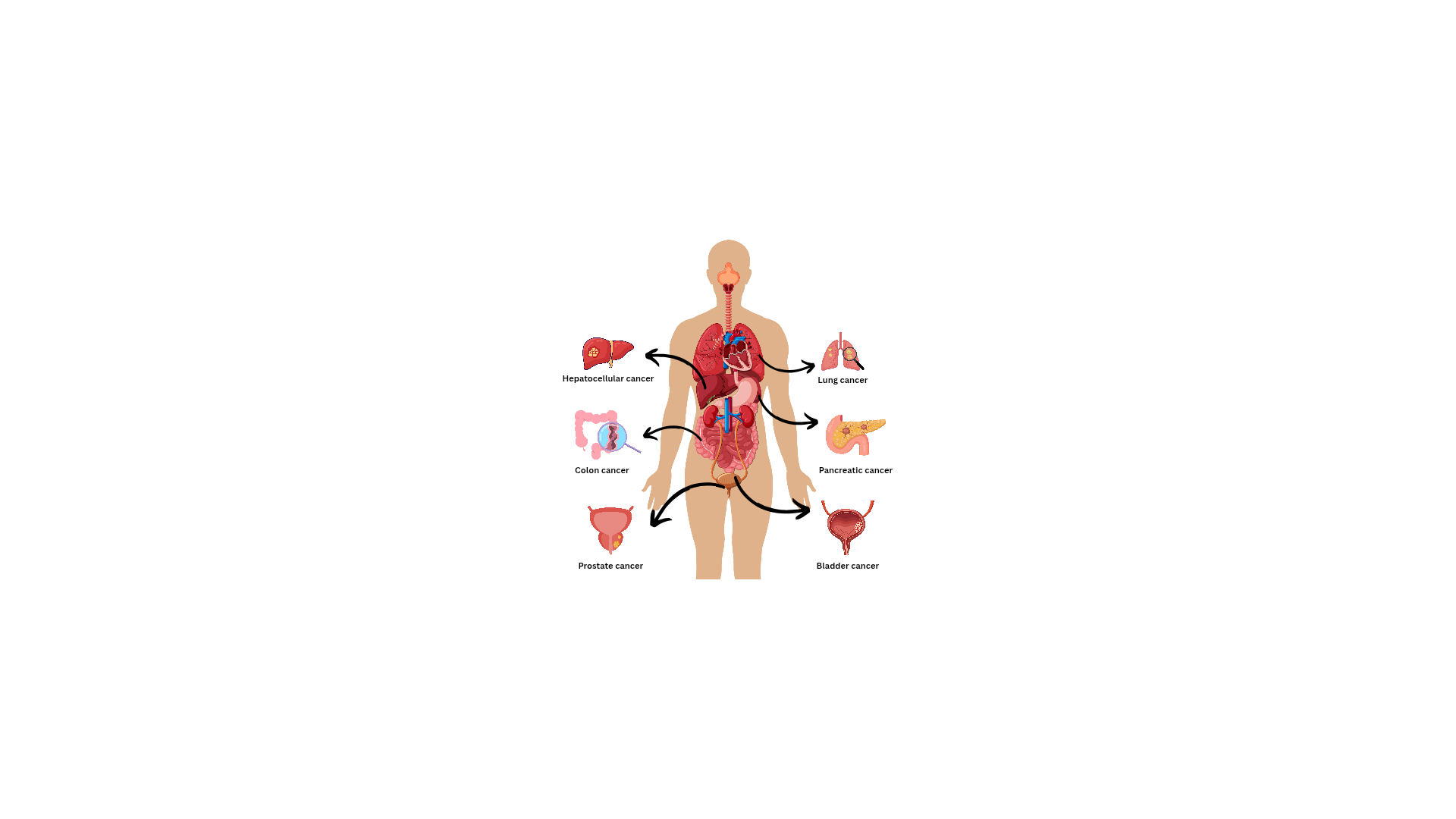
Urine contains several types of cells, including epithelial cells, kidney-derived cells, white blood cells (WBC), red blood cells (RBC), and urothelial cells, as well as genetic material, proteins, peptides, and inorganic compounds.

**Figure 1:** Urine have different types of cells, like WBC, RBC, urothelial cells, mRNA, ctDNA, and some inorganic compounds.

Each biomarker has benefits and drawbacks, and the choice of biomarkers may be influenced by the sort of technology available [17]. Presence of any of these unusual components, resealed by body into the systemic circulation, can also be filtered by the kidneys and transmitted in urine. As a result, researchers and medical professionals are eager to use urine biopsies for the potential diagnosis of several diseases as well as several cancers including bladder cancer, prostate cancer, hepatocellular carcinoma, renal cell carcinoma etc. [18].

1. **Utility of urine as liquid biopsy**:

Being a relatively cell-free bio-fluid, urine contains large numbers of macro and micro substances, including different cellular components, protein, circulating genetic materials (ct DNAs), and extracellular vesicles (EVs). As detection and sensitivity of urine ctDNAs are almost comparable to blood ctDNAs, urine sampling has been considered as an alternative body fluid for disease-detection, follow-up study of the patients and also designing therapy based on that [19]. Genetic abnormalities analyzed from test are reported to be useful in many cancers including urothelial carcinoma [20], breast cancer [21], colon cancer [22], lung cancer [23] etc. Considering the utility of urine analysis as one of the important liquid biopsy methods, advantages of this process has been discussed below:



**Figure 2:** Study of genetic abnormalities in human body reported to be different cancers including Bladder cancer; Prostate cancer, Renal cell carcinoma; Hepatocellular Carcinoma (HCC); Pancreatic cancer etc.

* Compared to tissue or blood, collecting samples from patients' urine is less invasive and more convenient, particularly when it's necessary to collect samples repeatedly to track the progress of a patient's cancer or the effectiveness of a treatment. [24].
* Urine collection and large amount of urine preserve is one of the main issues in tissue biopsy and liquid biopsy materials.
* Collection of urine is more patient friendly, the reason for that it can be done anywhere and any places, unlike other body fluid or tissue access, which must be done any medical clinics or hospitals [25].

Although these sample will help us in liquid biopsy to studied cancer screening, tracking cancer recurrence, and evaluating the effectiveness of chemotherapy and radiation therapy.

1. **Analysis of Urine liquid biopsy for different cancers:**

Based on the available reports and profound advantages of urine biopsy in disease detection, urine analysis has been wildly used for cancer diagnosis among patients. In this review, profiling of urine components in detection of cancer of both urogenic and non urogenic will be discussed below.

* 1. **Urinary liquid biopsy for bladder carcinoma:**

One of the most common types of cancer in the world is bladder cancer (BCa). Additionally, a type of bladder carcinoma i.e, non-muscle invasive BCa has a 70% chance of returning, placing a significant burden on the healthcare system. The bladder must undergo repeated cystoscopic tests in bladder cancer patients to check for return of a tumor. The cause of these individuals' need to undertake these pricy, unpleasant, and invasive procedures is due to the lack of reliable urine-based diagnostics to identify bladder cancer noninvasively. Thus, the creation of a urine-based test for bladder cancer detection would be of great value to individuals and healthcare systems [11,26]**.** Several types of markers i.e, protein based and cell-based markers are now a days havebeen evaluated for the detection of BCa in urine-based detection.

* **Nuclear Mitotic Apparatus Protein (NMP) 22:**

The nuclear mitotic apparatus protein (NMP) 22 is essential for the distribution of chromatin to daughter cells during mitosis and is found in all cells [27]. Patients with bladder cancer frequently have NMP 22 levels in their urine that are up to 25 times above normal. In quantitative assay NMP22 was actually identified, but it has produced into an immune-chromographic, Qualitative point-of-care assay which was needed only four drops of void urine. Within 20-50 minutes results are obtained whether it is positive or negative. According to US-FDA approved qualitative assay commit it helpful in the clinical setting because it does not need any certified pathologist to illustrate the results. Other benefits of NMP 22 include low cost, lack of patient preparation, independence from intact cells, and minimal interpretation time [28-29].

* **BTAstat™ & BTA-TRAK™:**

The original bladder tumor antigen (BTA) test is a latex agglutination test that looks for complexes related to the breakdown of the basement membrane. BTAstatTM and BTATRAKTM, two new iterations of this test, are intended to identify the complement factor H-related protein in excreted urine [30]. The FDA has approved BTAstat for the surveillance (monitoring) of bladder cancer in conjunction with cystoscopy but not for the screening or diagnosis of the disease. BTAstat is an immune chromographic, qualitative point-of-care assay that requires only five drops of urine, much as NMP 22. Positive or negative results are obtained anywhere between five and thirty minutes afterwards [31-32]. Similar to this, the BTA-TRAK test is a regular ELISA test that quantifies the human complement factor H-related protein. Urine stabilization is required for this test. BTAstat is more helpful in the clinical situation since it produces results quickly [33].

BTAstat shows enhanced sensitivity in high-grade malignancies, with a median sensitivity of 58% (range: 29-74%). In comparison to BTAstat, BTA-TRAK had greater sensitivity in high-grade tumors, with a median sensitivity of 71% (interquartile range: 60–83%) [34-35].

* **UroVysion™:**

The FDA has authorized UroVysion™ as a urine marker for both bladder cancer surveillance and diagnosis. Numerous investigations have amply demonstrated UroVysion's capacity to identify recurring illness despite negative cystoscopic findings. In 35–63% of individuals with a normal cystoscopic exam and a positive UroVysion test, disease recurrence can be predicted [37]. The reported sensitivity for UroVysion ranges from 36 to 65% for low-grade and low-stage bladder cancer. In comparison, UroVysion has a detection sensitivity for high-grade and high-stage bladder tumors that varies from 83 to 97% [38].

Table 1: Bladder cancer surveillance and diagnosis

|  |  |  |  |
| --- | --- | --- | --- |
| Cancer | Analyte | Target | Test |
| Bladder | peptides | NMP22 | NMP22 Bladder Chek |
| protein | Human complement factor H  related protein | BTA stat & BTA Trak |
| DNA | Aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus | UroVysion |
| mRNA | UPK1B, IGF2, CRH, ABL1 | Xpert® Bladder Cancer Detection |
| Tumor | cell DNA FGFR3 and TERT promotor mutations. | Uromonitor |

* 1. **Urine cytology and urine pH:**

Urine Cytology is a diagnostic method to detect malignant cells in the urinary tract. This conventional, non-invasive method includes microscopic examination of exfoliated urothelial cells in voided urine which allows pathologists to detect cellular atypia that indicates high-grade urothelial carcinomas, such as bladder cancer [39]. Urine cytology offers high specificity (over 90%) for high-grade tumors, but its sensitivity is limited for low-grade lesions that often shed less morphologically distinct cells [40]. Though there are some limitations, urine cytology is still a valuable tool in conjunction with the cystoscopy and is routinely used in cancer surveillance and follow-up protocols.

Urine pH, the measure of the acidity or alkalinity of urine, typically ranges from 4.5 to 8.0 in healthy individuals. Urine pH solely is not diagnostic of cancer; it can reflect underlying metabolic changes associated with the malignancy. Tumor metabolism leads to altered acid-base balance in patients due to increased glycolysis and lactic acid production (Warburg effect), which may result in acidic urine in several cases [41]. On the other hand, alkaline urine affects the stability and detectability of many important urinary biomarkers, particularly proteins and nucleic acids, making pH an important pre-analytical variable in urine-based cancer diagnostics [42].

Overall, urine cytology provides morphological evidence of malignancy and pH reflects metabolic shifts; both parameters contribute important context within broader urine biomarker profiling strategies for the cancer detection.

**4.2**: **Urinary liquid biopsy for prostate cancer:**

Prostate cancer (PCa) is the second most common disease to be diagnosed in developing countries and the third most prevalent cancer-causing death in men [43]. There are particularly specific issues with the diagnosis and prognosis of PCa, due to frequent histologic heterogeneity. In order to identify PCa, the Prostate serum antigen (PSA) level has been widely employed as a biomarker. Nevertheless, a significant number of men undergo needless prostate biopsy procedures each year as a result of PSA testing's high incidence of false positives caused by the physiology of the prostate [44-45]. Therefore, there is an urgent need for a non-invasive, affordable, effective, and reasonably accurate test for PCa early detection. Regarding this purpose, urine-based detection of prostate cancer would be one of the best plausible approaches to identify the predictive biomarkers for PCa. Now-a-days, a variety of markers, including DNA, RNA and protein-based bio- markers, have been studied for the identification of PCa in urine-based tests.

* **DNA Markers:**

It has been extensively documented in tissues that methylation of cytosine at CpG dinucleotides indicates an epigenetic change in prostate cancer (PCa) and is a viable area for the creation of urine biomarkers. Numerous techniques, such as methylation-specific polymerase chain reaction (MSP), bisulfite sequencing, methylation-sensitive single-nucleotide primer extension (MS-SNuPE), and combined bisulfite restriction analysis (COBRA), can identify aberrant DNA methylation in urine as well as tissue samples [46]. Glutathione-S-Transferase P (GSTP1), a gene involved in the detoxification of electrophiles and other harmful elements, is one well-known DNA methylation target. Numerous studies have demonstrated GSTP1 hyper-methylation in PCa patients' urine samples. Several experimental reports showed that the sensitivity of GSTP1 in urine was low that ranging from 21.4% to 38.9%. According to these findings, patients with increased PSA levels should get a supplemental GSTP1 methylation test before deciding whether to perform subsequent biopsies or not [47].

* **RNA Markers:**

The biggest amount of RNA urine indicators has been developed therapeutically to date. The prostate-cancer-specific gene PCA3 (PCa Antigen 3) was identified in 1999 by Busse makers and Issacs and has since received substantial examination [48]. 95% of primary PCa specimens show a 34-fold rise in PCA3 expression, which is overexpressed. As there is no protein product found for PCA3, hence RTPCR platform was developed and wildly used for analysis of PCA3 from urine [49]. The commercial platform is now called the Progensa® PCA3 assay (Gen Probe), which involves prostate specific (PSA) transcripts as an internal control for RNA quality and to establish the presence of prostate specific nuclear material. The PCA3 score is created by the PCA3 to PSA ratio. The test does not evolve to be vastly influenced by age, inflammation, trauma or importantly, prostate volume. The FDA has officially announced PCA3 for its use in predicting Cancer in patients with increase PSA levels and results of the biopsy should be Negative [45-46].

* **Protein Markers:**

Proteins are often discharged into physiological fluids, unlike DNA and RNA, and their detection does not always require the presence of cancer cells. Additionally, immunologic tests like ELISA, and the most common instruments for quantitative protein measurement, are reasonably priced, sensitive, and simple to build.

Table 2 : List of Protein Markers

|  |  |  |  |
| --- | --- | --- | --- |
| Cancer | Analyte | Target | Molecular Profile |
| Prostate | DNA Marker | Glutathione-S-Transferase P (GSTP1) methylation | Hyper-methylated in PCa |
| RNA Marker | prostate-cancer-specific gene PCA3 (PCa Antigen 3) | Overexpressed |
| Protein Marker | Bladder tumour fibronectin (FN1), Urinary prostate specific antigen (PSA), Vascular endothelial growth factor (VEGF) | Overexpressed |

**4.3**: **Urinary liquid biopsy for Renal Cell Carcinoma:**

Renal cell carcinoma (RCC) is the ninth most prevalent cancer worldwide and even more so in developed nations (up to 6-8% of all cancers). Its prevalence peaks between the ages of 60 and 70, with a 3:2 male to female ratio [50-51]. Since most renal tumors do not manifest symptoms until the advanced stages of the disease, diagnosing renal cell carcinoma can be challenging. It is uncommon (6–10%) to experience the classic trio of flank pain, palpable abdominal mass, and gross hematuria at the same time, and this is usually the case when the histology is aggressive [52]. Considering these difficulties, detection and better therapeutic management of RCC demands identifications of rapid, easily accessible biomarkers from excretory products of kidney i.e, urine. To the best of our knowledge, very scanty literature is available on the identification of urine-based biomarkers in RCC. So, this review seeks to detail the comprehensive information about the predictive urinary biomarkers for better identification and handling of RCC.

* **Nuclear Mitotic Apparatus Protein (NMP) 22:**

The nuclear mitotic apparatus protein (NMP) 22 is a potential indicator of malignant cells due to their properties, which include aberrant genetic material dispersion and accelerated mitosis. Numerous NMPs have organ-specific properties. Breast, colon, bone, and urothelium have all been found to have cancer-specific NMPs, and NMP-22 has been discovered as a potential urothelial-specific cancer marker [53]. Like bladder cancer, level of urinary NMP-22 levels was significantly higher in RCC patients compared to the patients with kidney stones and simple renal cysts used as control group, reported by *Kaya et al* [54].

* **Neutrophil Gelatinase-Associated Lipocalin (NGAL):**

Lipocalin 2, a well-known member of the lipocalin family, is commonly referred to as Neutrophil Gelatinase-Associated Lipocalin (NGAL). The lipocalins are a large group of tiny, mostly extracellular proteins that were originally thought to be unrecognized transporters of hydrophobic ligands [55-56]. NGAL which is expressed in the kidney's epithelial cells, is a factor in kidney formation. NGAL is a biomarker of tubular injury that is expressed in several renal tumor histotypes, especially in papillary RCC [55]. According to the *Di Carlo* and *Morrissey et al.* demonstrated that the mean value of urinary NGAL in patients with cRCC was higher than that found in the urine of the control group. However, no further co-relation was found with tumor size or stage [56-57].

* **Other cellular biomarker related to RCC:**
* **Kidney Injury Molecule 1 (KIM-1) -** A wide range of acute and chronic kidney illnesses can be diagnosed using the urine biomarker known as kidney injury molecule-1 (KIM-1). KIM-1 is a diagnostic marker for renal cancer, although despite having diagnostic sensitivity for kidney cancer, it is widely recognized that it also reflects a variety of kidney ailments [58]**.**
* **Aquaporin-1 (AQP-1) and Perilipin 2 (PLIN2) -** The tissue from surgically removed renal tumors has been found to overexpress aquaporin-1 (AQP-1) and adipocyte differentiation-related protein (renamed Perilipin 2 (PLIN2)) [59]. *Morrissey et al*. discovered that patients with clear cell and papillary carcinoma had higher urine concentrations of AQP-1 and PLIN2 than controls, based on the possibility that these upregulated proteins could be excreted or eliminated through the urine [60].

Additionally, the urine concentration had no discernible impact in non-cancerous kidney condition such as glomerulonephritis, diabetic nephropathy, and urinary tract infection by these two indicators, which represent the tumor size and stage [61].

**4.4**: **Urinary liquid biopsy for Hepatocellular Carcinoma:**

Hepatocellular carcinoma (HCC) is mostly found in Southeast Asia and sub-Saharan Africa; it is a fifth most common cancer and third propulsion to causing cancer diseases. The morbidity and death rate of liver cancer remain high despite major advancements in cancer diagnosis and therapy because early detection is still difficult [62-63]. Therefore, there is an urgent need for early detection biomarkers that could serve as HCC treatment targets. Regarding this purpose, urine-based detection of HCC predictive biomarkers is one of the most logical methods. Three key features are required for a urine biomarker to be broadly applicable. First, the biomarker creates pre-renally, be sufficiently tiny and have ionic charge to pass through the renal glomerulus and not be taken by the renal tubules. Although its molecular weight must be approximately less than 20KDa [66]. Second, the marker should be unique the cancer in question and related to how cancer impact on physiology. The biomarker also releases in maximum quantities to allow for precise, reproducible detection of early illness. Large, complex proteins are not good candidates for urine biomarkers because they are not likely to enter the urinary stream [67]. Several cellular proteins like TGF (alpha and beta forms) and Neopterin are reported to be elevated in HCC [68]. On the other hand, Urinary trypsin inhibitor (UTI) is a 25 kDa protein thought to be produced by hepatocytes, was reported to be elevated in HCC patients compared to cirrhosis patients by enzyme-linked immunosorbent assay-based study [69-70].

**4.5: Urine DNA Biomarkers in Hepatocellular Carcinoma:**

Hepatocellular carcinoma is one of the most crucial heterogenous diseases which is caused by many genetic alternations, Thus, it needed cluster of multiple biomarkers obtain high screening sensitivity. Urine contains low molecular weight DNA (~1-2 nucleosome sized) or cell free DNA (cf DNA) derived from apoptotic cell throughout the body [71]. HCC marker is detectable in urine and circular tumour DNA (ctDNA) which have crucial role in HCC. In PCR analysis detect circulation derived gene alternation in urine [72]. Eight Candidate markers, mutated codon 249 TP53 and CTNNB1 Codons 32-37 and aberrantly methylated DNA of Six genes (*RASSF1A, GSTP1, CDKN2A, SFRP1, TFPI* and *MGMT*) [71-72]. This is the largest study to report the use of urine based ctDNA biomarker to screen of for HCC. The use of ctDNA in blood as a liquid biopsy for cancer detection has been studied extensively for decades but is limited by low sensitivity. Studies have reported the detection of plasma ctDNA alternation and protein markers in serum identify the early stage of HCC [72]. The detection of urinary DNA biomarkers is possible to find out by different diagnostic methods (Serum AFP and MRI Imaging) for the detection of HCC recurrence.

Lastly, DNA biomarker identification in urine may also be useful to monitoring effectiveness of cancer treatments that induces the apoptosis of tumor cells. Circular tumor DNA found in urine was mostly from apoptotic tumor cells. Thus, HCC often shows being the multi clonal origin. In conclusion, urinary DNA biomarker testing may have potential for the early detection of HCC recurrence [73]. This urine DNA biomarker test can overcome the different inherent technology for identifying mutated genes like TP53 and CTNNB1 and other biomarker genes and to provide a highly sensitive tool to monitoring HCC recurrence.

**4.6**: **Urinary liquid biopsy for Pancreatic Cancer (PCa):**

One of the most aggressive and fatal cancers is pancreatic ductal adenocarcinoma (PDAC). PDAC patients had a median survival of 5–6 months and 5-year survival rates of roughly 9% have been reported internationally, with over 80% of cases being identified at advanced stages [74]. However, the 5-year survival rate can be significantly increased, up to 32%, if PDAC is discovered earlier, when it is still localized [75-77]. There are currently no effective biomarkers for the earlier identification of PDAC, and the only one in clinical use i.e., blood CA19-9, is insufficiently sensitive or specific for screening purposes [78-80]. Considering these limitations, urine represents a promising alternative biological fluid that enables for fully non-invasive sampling and simple repeated measurements. Previous studies reported that both REG1A and REG1B were found as prospective candidates for urine biomarkers with REG1B exhibiting superior differential [81]. Other group of studies stated that several other cellular proteins like LYVE1, TFF1 showed elevated expression in PDAC patients compared to control group and exhibited 26% and 15% of sensitivity respectively [82-84].

1. **Conclusion and Future Perspective:**

A modest tumour burden of urological and non-urological cancers can be detected by changes in genomic and genetic material in the urine, which may occur prior to changes in imaging. Standardized processes and normalization procedures are still necessary. The current urine-based strategy still needs extensive investigation for prospective validation by large cohorts despite the non-invasive sample collecting method's potential benefits. Urine biomarkers are a fascinating new technology, but it's crucial to know if they provide better disease recurrence profiling and if therapies led by elevated urine biomarkers actually result in better outcomes.

**Author contributions:** RB and RG wrote the manuscript. RG and SD prepared the figures. JC, SS, SM, and CM revised the full article, corrected where necessary. All authors reviewed the final manuscript.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models were used to write or modify this manuscript.

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