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Recent Developments of Biomarkers in Diagnosis of Genitourinary Cancer Using Liquid Biopsy

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Abstract

The high mortality and recurrence rates of genitourinary (GU) malignancies, which include bladder, prostate, renal, testicular, penile, and adrenal tumors, pose serious clinical problems. Foe better results, early detection is essential, yet conventional diagnostic techniques frequently have little sensitivity and are instructive. Non-invasive methods have become viable substitutes for the identification, tracking, and treatment of malignant tumors, especially urine liquid biopsies. Early bladder cancer (BC) diagnosis may be possible with urinary biomarkers such as cytokeratin's, FGFR3, NMP22, BTA, and miRNAs (e.g., miR-126, miR-141-3p). While miRNAS and exosomal content provides information on the molecular mechanisms underlying the disease and its response to treatment, methylated DNA markers (such as DAPK and TERT) also aid in the diagnosis of BC. The predictive and diagnostic potential of urine biomarkers are being improved by developments in metabolomics, multi-omics, and epigenetic studies. Though problems like tumor heterogeneity, biomarker standardization, and false positives still exist, methods like electrochemical biosensors, real-time PCR, and quantitative methylation-specific PCR are increasing the biomarkers detection sensitivity and specificity. Exosome analysis combined with cutting-edge bio sensing technologies opens up new possibilities for customized medicine in the diagnosis and treatment of BC. Resolving these issues and improving clinical results for patients with GU cancer require ongoing innovation in biomarker research and diagnostic technologies.

Keywords: Urinary Biomarkers, Exosomes, Biosensors, Liquid Biopsy, Multi-Omics

Introduction

Genitourinary cancer is a urinary system cancer which infects both male and female; it also infects reproductive organs as well in both male and females. Genitourinary cancer is a disease which forms when abnormal cells grow in the prostate, bladder, kidney, testicular, adrenal gland, penile, or other parts of the urinary tract system [1].

The 6th most frequent cancer in worldwide is genitourinary cancer. The world health organization (WHO) reports that genitourinary cancer claimed 200,000 lives globally in 2018 and that there were 549,000 new cases.

A major concern is that non-muscle invasive bladder cancer (NMIBC), the most prevalent type of bladder tumour, has one of the highest recurrence rates, with up to 70% of patients facing at least one recurrence [2].

Malignancies of the genitourinary system (GU), includes bladder, kidney (renal), penis, and testicular cancers. In united states prostate cancer is the most prevalent cancer diagnosed in men. The prevalence of GU cancer is higher in men compare to women, and bladder cancer is three times common in men compare to women [3].

In the USA, 444,660 newly diagnosed cases of genitourinary cancer are anticipated to occur in 2022, accounting for 67,330 fatalities and 23% of all cancer cases. About 11% of all cancer-related deaths nationwide [4]. genitourinary cancer is most commonly occurs in the prostate, bladder, and kidney, testicular, penile, and adrenal tumors are less prevalent [5].

Prostate cancer

The prostate is a small glandular organ, typically weighing 20-30 grams in healthy adult male, and it plays a key role in producing most of the seminal fluid. Positioned in front of the rectum nerves known as the "nervi erigents" which are essential for continence and erectile function, run from the hypogastric plexus and closely align with the prostate's pesto lateral surface. This anatomical relationship is crucial when assessing potential side effects of prostate cancer treatments. McNeal's 1968 classification of the prostate's zonal anatomy remains widely used, with 70-80% of cancers developing in the peripheral zone, while cancer rarely occurs in the central zone [6].

Epidemiology

Prostate cancer (PC) is the second most common cause-related deaths among men in the United States. The American Cancer Society estimates that there will be 1,466,718 new cases of PC globally in 2024 [7].

Prostate cancer is the second most common cause of cancer related death in men. In 2020, PC was the most prevalent cancer identified in 122 countries, with almost 1.4 million new cases and 375,304 deaths worldwide, according to GLOBOCAN 2020 estimates. Prostate cancer is the second leading cause of cancer-related death among men. In 2020, prostate cancer identified in 112 countries, with almost 1.4 million new cases and 375,304 deaths worldwide, according to GLOBOCON 2020 forecasts [8].

Bladder cancer

Bladder cancer, a common malignancy of the urinary system, develops in the tissues of the bladder, a hollow organ responsible for urine storage. The most common kind is urothelial carcinoma, accounting for more than 90% of occurrences in industrialized nations. This type of cancer is most common in elderly people, and risk factors include smoking, chemical exposure, and persistent bladder inflammation. Symptoms such as gross or microscopic hematuria, urine frequency, and pelvic pain lead to its discovery [9].

Urothelial carcinoma occurs through two different routes. The first is largely concerned with papillary neoplasms, and the second with flat or sessile lesions.

Non-muscle-invasive bladder cancers (NMIBC) are low-grade papillary tumors that develop from simple hyperplasia and/or mild dysplasia. This group also contains carcinoma in situ (CIS), a high-grade, superficial malignancy. NMIBCs have the following characteristics: Mutations that activate fibroblast growth factor receptor 3 and inactivate STAG2 are discussed. The alpha isoform of phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit. Loss of heterozygosity on chromosome 9. Telomerase reverse transcriptase.

In around 10% of cases, low-grade papillary NMIBC progresses to a muscle-invading malignancy due to cyclin-dependent kinase inhibitor 2A loss [10].

Muscle-invasive bladder cancer (MIBC) results from flat dysplasia or carcinoma in situ and is distinguished by the the lesions contain TP53 mutations as well as chromosome 9 heterozygosity loss. Invasive carcinoma can then develop metastatic potential through RB1 and PTEN loss, as well as other changes. Copy number changes and genomic instability are associated with tumor growth and a poorer prognosis. NMIBC typically has diploid or near-diploid karyotypes as compared to muscle invading. MIBC is typically aneuploid, with many chromosomal aberrations [11].

Urinary bladder cancer is a common kind of cancer that affects the urinary tract. According to recent reports from India's National Cancer Registry Programme, the annual incidence rate of urinary bladder cancer is 2.25 per 100,000 people. 1 The incidence rate is 3.67% in men and 0.83% in women. 1,2 Bladder cancer is the ninth most common type of cancer worldwide, with around 356,000 new cases recorded each year.Globally, urothelial cancer is the most frequent type of bladder cancer, accounting for around 90% of occurrences, with 80% being non-muscle invasive and low grade, but with a 50% recurrence rate. 3,4 This is followed by squamous cell carcinoma (5%), and primary adenocarcinoma (2%). Muscle-invasive urothelial malignancies make up about 20% of all cases and are often caused by high-grade dysplastic or carcinoma in situ lesions. Adenocarcinoma and squamous cell cancer cases, on the other hand, are typically muscle invasive at the time of diagnosis and have a worse prognosis than urothelial cancer. The histological distribution in India appears to be comparable to that described globally, despite the fact that studies with small sample sizes have been conducted due to a lack of large-scale literature on the histopathological distribution of bladder cancer in India [12].

Renal cancer

Epidemiology

Renal carcinoma, one of the most common malignant tumors of urinary system, has a poor prognosis and has been increasing recently. According to the latest figures, there were 431,288, new cases of renal cancer and 179,368 new renal cancer related deaths worldwide in 2020. Compared to 2018, kidney cancer incidence and mortility rates increased by 7.5% and 5.6%, respectively, in 2020. Renal cell carcinomas, a group of various cancers that arise from renal tubular epithelial cells, account for about 90% of all renal malignancies [13].

Nearly 90% of adult instances of kidney cancer are renal cell carcinoma, sometimes referred to as hypernephroma or Grawitz tumor. Renal pelvic transitional cell carcinomas are another kind that behaves similarly to bladder cancers. Renal sarcoma is another rare kidney malignancy. The main focus of thus review will be renal cell carcinoma (RCC), which accounts for almost 3% of all adult malignancies and has several histological subtypes. People between the ages of 50 and 70 are most commonly found to have this older age group tumor. The ratio of men to women is about 2:1 [14].

An estimated 295,000 cases are diagnosed annually, out of an estimated 134,000 cases recorded world wide. In 2018, there were an estimated 65340 new cases and 14970 yearly deaths in united states. The male to female ratio is more than two to one. In terms of the number of years lost, RCC was ranked twenty among both sexes in the 2017 list of malignancies, down from its 2007 ranking of nineteenth. Given that the typical age at diagnosis should prompt a search for an underlying genetic predisposition (syndrome). Incidence has been associated with rising obesity rates. It has been shown that decreasing mortality rates are associated with improved treatment options [15].

Testicular cancer

Testicular cancer is the most common cancer in men aged

15 to 45. It is also one of the most common tumors that can be cured if cough early and treated with a range of methods. It is responsible for 1% of tumors in men and 5% of urological malignancies. Due to the long-term impact that testicular cancer and its treatment can have on a patient's life, the disease has become more prevalent in recent years and has become more prevalent in recent years and has gained greater attention. Over the past forty years, testicular cancer has become more common. With appropriate treatment, the prognosis is favourable, with a five-year survival rate of over 95% and a cure rate of over 90% [16].

The new cases if testicular malignancies retrieved from GLOBOCAN 202 database in order to look at current incidence and mortality trends. Testicular cancer was the most prevalent cancer among men between the ages of 15 and 44 in 62 counties globally in 2020 [17].

Penile tumor

Penile cancer is a rare cancer that can be challenging for medical professional to treat and takes a terrible psychological toll on its victims. Patients with this illness may delay seeking care due to feelings of guilt, shame, fear, neglect, and denial. Additionally, the lesions are typically painless and do not typically cause erectile dysfunction or issues voiding in their early stages [18].

In 2020, 36,068 new instances of penile cancer were detected worldwide, according to the international agency for research on cancer of these, 95% were squamous cell carcinomas. Penile cancer is more common in less resource rich parts of the world, like Africa, Asia, and South America, penile cancer may account for as much as 10% to 20% of all male cancers in these areas. The increased risk may be caused by differences in hygiene practices, the high proportion of uncircumcised men in these communities, and HPV and HIV infections [18].

Adrinal tumor

The adrenal is an endocrine organ that has two physiological functions. The outer adrenal cortex produces a variety of steroid hormones, including mineralocorticoids like aldosterone and the androgen dehydroepiandrosterone, and glucocorticoids like cortisol [19].

The office of rare diseases research at the national institutes of health reports that there are less than 200,000 occurrences of adrenocortical carcinoma in the United States, with an incidence of 0.72 cases per million in the United States and 0.5 to 2 cases per million globally. The annual death ratee from adrenocortical cancer in the US is 0.2%. Adults in their fourth and fifth decades of life experience it, whereas children under five experience a lesser peak. With a female to male ration of 2.5 to 3 to 1, it disproportionately affects women. The development of ACC was linked to the use of oral contraceptives and cigarette smoking in a 1996 study that evaluated risk factors [19].

Importance of early detection

Cancer poses a major threat to human life and is very deadly disease. Cancer prevention, detection, and treatment involve crucial components such as post treatment patient monitoring, assessing the effectiveness of cancer treatments, and the immediately alert patients to the risk of tumour metastasis and recurrence. There is currently no viable biomarker for early cancer diagnosis because of the complexity of tumour incidence and tumour heterogeneity, despite a great deal of study in this field and the development of numerous technologies aiming at the early identification of tumour biomarkers from diverse clinical samples. Rather, there is a lot of potential and success with other tumour liquid biopsy [20].

For genitourinary malignancies, the majority of diagnostic and prognostic methods are invasive and have extremely poor sensitivity and specificity. Given the high rates of disease and death linked to genitourinary malignancies, it is crucial to design policies that biomarker-based clinical non-invasive testing for illness monitoring, therapy, and early disease detection response tracking [21].

Because there are not many sensitive prognostic biomarkers, a large portion of genitourinary cancer patients are usually discovered at an advanced stage, and as a result, the 5- year survival rate is still far from optimal. In light of this, scholars worldwide have aimed at improving patient survival by identifying new tumour biomarkers linked to genitourinary cancer screening, diagnosis, prognosis, and therapeutic efficacy assessment. A quick shift in diagnostic modalities has been observed with the introduction of novel biomarkers and clinical validation of new diagnostic instruments [21].

The key to a successful cancer treatment is early detection; however, early lesions can only discharge a limited number of biological signs due to physiological and mass transport constraints. On-going research's main goal is to identify intrinsic biomarkers by analysing blood and bio fluids. Bioengineered sensors and synthetic markers are being developed to increase specificity [24].

Challenges in early detection and current diagnostic methods

Improving patient's outcomes and reducing the severity of the disease depend on early cancer identification. In its early stages, cancer is difficult to identify with conventional techniques since it frequently exhibits no symptoms or very mild ones. There is an increasing need to create sophisticated diagnostic methods that allow for the detection of cancer in its earliest, most curable stages hence increasing the likelihood of a successful intervention and survival [22].

The current state of early cancer diagnosis is characterized by serious difficulties using conventional diagnostic techniques. Although methods like imaging and tissue biopsy have been useful in the diagnosis of many types of cancer, they frequently don't have the sensitivity and specificity needed to identify cancer in its early stages. These methods have drawbacks, such as the possibility of false positive or negatives and their incapacity to identify minute molecular alteration suggestive of early stage illness [22].

In addition a lot of diagnostic instruments available today may be intrusive, which could cause discomfort for patients and occasionally discourage early screening. The development and application of more sensitive and targeted methods that make use of state of the art technologies, including multi omics, are urgently needed in light of these constraints in order to decipher the molecular complexities of cancer and provide more precise and early diagnosis [22].

Role of biomarkers in GU cancer diagnosis and management

The main areas of study interest for biomarkers are their potential to detect treatment resistance, predict response to

systemic therapy, and prevent toxicity. Biomarkers that identify mutant tumor suppressor genes, changed signaling pathways, and abnormally expressed molecules aid in the selection of patients who may respond to a particular treatment. In this sense, biomarkers greatly enhance patient's quality of life while also improving results and lowering expenses associated with inefficient treatments [23].
Creating low-cost, highly sensitive and specific, non-invasive biomarkers that may also be helpful for the patient's prognosis and monitoring is of great interest currently [35].
There is justification for creating molecular biomarkers for early detection and disease prevention since epigenetic changes are thought to happen early in tumor development and may occur before genetic changes. The development of sophisticated technology that can now identify epigenetic modifications throughout the genome holds great potential for improvement our ability to create biomarkers for early cancer identification [35].

Defination and types of biomarker

Biological molecules in blood, bodily fluids, or tissues that reveal whether a process, condition, or disease like cancer is normal or aberrant is how the national cancer institute defines biomarker [24].
Genetic mutations, transcriptional changes, and post-translational modifications can all be blamed for changes in them, which are crucial for differentiating between people with and without the disease. The several chemicals that comprise a biomarker include proteins, nucleic acids, peptides, and antibodies, to name just two. Proteomic profiles, metabolomics signatures, and gene expression patterns are only a few examples of the various combinations of alterations they can contain. The identification of biomarkers can be done non-invasively using physiological fluids such as blood, urine, saliva, sweat, cerebrospinal fluid (CSF),or a tissue sample obtained by biopsy and imaging [24, 33].

Advantages of urine as a non-invasive sample.

Urine can reveal important details about many kinds of illnesses and is a very sensitive and non-invasive biomarker [25].
Urine biomarkers can provide early detection of a wide range of diseases and help clinicians diagnose and treat them better. With continued research, urine has the potential to become a powerful and cost-effective tool for diagnosing and monitoring various diseases [25].
Liquid biopsy has been used extensively for a variety of cancers. By adopting a simple technique, it can obtain tumour genomic information early on and avoid the complexities of tissue biopsy [26].
Many tumor-associated biomolecules can be released by tumor cells into bloodstream, where the glomerular filtration barrier may filter some of them into urine. Additionally, BC's unique physiological makeup permits tumors to come into direct contact with urine [26].
Because liquid biopsies are noninvasive and simple to repeat, they are steadily gaining popularity as a diagnostic and prognostic method for patients with lung cancer. This method specifically enables real-time patient monitoring throughout treatment and the identification of various genetic changes that may be responsive to targeted therapy or linked to treatment resistance. Additionally, it makes biomarker assessment quickly accessible [27].

Types of urinary biomarkers

Table1: List of urinary biomarkers [29]

Candidate Biomolecules for Bladder Cancer Detection	Biomarkers for Bladder Cancer Detection	FDA Approved Biomarkers for Bladder Cancer Detection
• miR-126 • miR-141-3p • NMP22 • FDP • IL-8 • hOGG1 • COX-2 • BTA • BLCA-1 • Cytokeratin 8, 18, 19 • APOA-1 • APOA-2 • FGFR3P53 • CDK1 • miR-26-a • miR-191 • OSR1 • SIM2 • CCL18	• miR-126 • miR-141-3p • NMP22 • FDP • IL-8 • hoGG1 • COX-2 • BTA	• NMP22 • BTA (Complement factor H-related protein) • Carcinoembryonic antigen two mucins

Table 2: Urine-based biomarkers for detection and surveillance of bladder cancer

Biomarkers	Function	Sensitivity	Specificity	Reference
Nuclear mitotic apparatus protein 22 (NMP22)	Nuclear matrix protein/part of nuclear frame	47-100%	60-90%	[43]
Bladder tumor antigens (BTA)	Interruption of the complement cascade/cell growth	BTA stat test, 57-83%; BTA TRAK test, 66-70%	BTA stat test, 60-92%; BTA TRAK test, 65-75%	[43]
Urine bladder cancer (UBC) tests	Cytikeratin 8 and 18 fragment detection/part of the framework	Great variation, no reliable data available yet	Great variation, no variable data available yet	[43]
uCyt+/ImmunoCyte	Detection of tumour-associated cellular antigen	50-100%	69-79%	[43]
UroVysion	Detection of aneuploidy in chromosomes 3, 7, 12 and loss of the 9p21 locus of the p16 tumour suppressor gene	70-80%	80%	[43]
Survivin	Antiapoptotic protien	64-83%	88-93%	[43]
BLCA-1 & BLCA-4	Nuclear transcription	BLCA-4, 84-96%; BLCA-1, 80%	BLCA-4 up to 100%; BLCA-1, 87%	[43]
CYFRA 21-1	Detection of fragments of cytokeratin 19 (fimament protiens, specific for epithelial cells)	85%	82%	[43]

Table 3: Methylation-based biomarkers for the detection/diagnosis of cancer

Cancer type	Marker	Sensitivity	Specificity	Biosample	Method	Reference
Prostate	*GSTP1*	75.0%	98.0%	Urine	Real-time PCR (rtPCR)	Joe *et al.* [35]
prostate	*GSTP1, APC*	95-100%	NA	Urine	Quantitative methylation-sensitive PCR (qMSP)	Jotkoe *et al.* [40]
prostate	*PLA2G16* CpG island	92.0%	94.0%	Urine	Pyrosequencing	Jarrad *et al.* [41]
Bladder	*DAPK, BCL2 & TERT*	21.6%-64.9%	78.4%	Urine	Quantitative methylation-sensitivePCR (qMSP)	Joe *et al.* [35]
Bladder	*POU4F2 & PCDH17*	90.0%	93.6%	Urine	Quantitative methylation-sensitive PCR (qMSP)	Wang *et al.* [42]
Bladder	*ONECUT2 & VIM*	87.1%	82.9%	Urine	Real-time PCR (rtPCR)	Joe *et al.* [35]
Bladder	*VIM, OSTM1, SLC4A10, AC092805.1 & ONECUT2*	87.2-90.5%	86.8-91.1%	Urine	Real-time PCR (rtPCR)	Joe *et al.* [35]

Table 4: Current methylation-based IVDs for the detection/diagnosis of cancer

Cancer type	Name	Markers	Sensitivity	Specificity	Biosample	Method	Reference
Prostate	epiCaPture	*GSTP1, SFRP2, IGFBP3, IGFBP7, APC & PTGS2, GSTP1, RASSF1 & APC*	73.00%	76.00%	Urine	qMSP	Joe *et al.* [35]
Bladder	Bladder EpiCheck	15 proprietary markers	68.20%	88.00%	Urine	MSRE-rtOCR	Joe *et al.* [35]
Bladder	AssureMDx	Methylation *OXT1, ONECUT2 & TWISTI* + mutation *FGFR3, TERT & HRAS*	93.00%	86.00%	Urine	SNaPshot assay & MSP	Joe *et al.* [35]

Protien biomarker

BTA

Currently, the FDA has approves two BTA assay for BCa initial diagnosis and surveillance: The quantitative BTA test (BTA-TRAK) and the qualitative BTA test (BTA-State). In contrast to BTA-TRAK, which is an enzyme-linked immunosorbent assay (ELISA) assay, BTA-State is point of care quick immunochromatographic assay that yield data in 5 minutes. Urinary qualitative BTA testing is authorized in a surveillance context in Japan. When human complement factor H-related protiens (hCFHrp) are present in urine, BTA assay can identify and quantify their levels [34].

By vaccinating mice with a partly purified protein from BCa patients urine, this protein was tested and found to be a BCa-specific antigen. However, hCFHrp is not exclusive to BCa; it is also expressed in kidney and prostate tumors. Therefore, false-positive results in BTA assay have been recorded due to inflammatory diseases and genitourinary malignancies. In one meta- analysis, BTA-Stat had sensitivity of 64% and specificity of 77%, whereas BTA-TRAK demonstrated a sensitivity of 65% and specificity of 74%. Because of this, BTA assay are more sensitive than cytology, but less specific. But compared to high-grade BCa (91%) assay, BTA assay shpw a lower sensitivity for low

grade BCa (36%). Consequently, there is little application of BTA tests in clinical settings [34].

The NMP22

The FDA presently approves two NMP22 tests for BCa initial diagnosis and surveillance: A quantitative NMP22 ELISA (NMP22 Bladderchek). For the initial diagnosis, NMP22 assays, both qualitative and quantitative, are authorized in Japan. Nevertheless, NMP22 Bladderchek's sensitivity for low-grade BCa is only 25%. Furthermore, isolated hematuria has a major impact on NMP22, and circumstances with elevated cell turnover, like urothelial tract inflammation, produce false positive results. The NMP22 Bladderchek shown poor performance in a meta-analysis, with sensitivity and specificity of 58% and 88%, respectively, but the NMP22 Bladder Cancer ELISA-Test demonstrated 69% and 77% respectively. NMP22 and BTA tests are therefore rarely used in clinical settings [34].

DNA/RNA Biomarkers

Methylated DNA potential for cancer diagnostics

Overview of Methylation in DNA

DNA methylation is one of the most resilient epigenetic markers on the human genome; DNA methylation can withstand the majority of storage and experimentation settings and can be taken from almost any tissue or physiological fluid. This resilience makes methylation a desirable marker for diagnostic development, as it does the stability of cell-free DNA in bodily fluids and the regularity of aberrant methylation in cancer. Furthermore, because methylation alterations are common throughout the genome, using numerous target sites in a single experiment enables higher detection sensitivity and specificity. For early identification and screening, these biomarkers should be highly specific yet sensitive to minimize false positives and needless follow-up tests [35].

miRNA

miRNAs are short non-coding RNAs that are 19-25 bps long. They primarily control gene expression and obstruct some cellular processes that produce proteins. Both RNA sequencing and polymerase chain reaction (PCR) techniques can identify miRNA, which are extremely stable molecules. In BC miRNA instability develops, which helps with the disease diagnosis and prognosis. BC patients urine, tissue, and blood samples all show signs of miRNA dysregulation. However, alterations in a panel of miRNAs can be regarded as BC biomarkers, whereas variations in a single miRNA level are not suggestive of BC [28].

According to Braicu *et al*., quantitative reverse transcription polymerase chain reaction (RT-qPCR) study showed that miR-139-5p and miR-143-5p down regulated in the Bladder cancer, whereas miR-23a-3p, miR-141-3p and miR-205-5p were increased [36].

miR-21, miR-18, 396-182, miR-205, and miR-210 showed increased levels, in BC in another study by Homami *et al*. However, miR-409, miR23b, miR-214, miR-29c, miR-124, and miR-5903p were suggested believed to have declined in the BC. Research has demonstrated that the majority of miRNAs associated with BC play a part in the p53 and fibroblast growth factor receptor 3 (FGFR3) pathways [37].

A urine miRNA peofile that predicts the presence of BC was discovered by Hofbauer *et al*. Let-7c, miR-135a, miR-135b, miR-204, and miR345 are the six miRNAs they anticipated might be utilized to differentiate between high and low grade BC in both the NIMBC and MIBC [38].

Metabolites: Metabolic profiling and its relevance

The goal of the widely accepted scientific field of metabolomics is to identify and measure the complete set of intracellular and extracellular metabolites (molecules with molecular weight less than 1500 Da), which represent the ongoing modifications of the comples structure of biochemical reactions in living systems to adjust to their surroundings and pathological occurrences. This covers measurements in biofluids such as tissue, biological extracts, serum, plasma, urine, cerebrospinal fluid, and exhalations. This study of how molecules make up a cell tissue or organism is approached holistically by ecology disciplines including metabolomics (metabolites), proteomics (protein), transcriptomics (mRNA), and genomics (genes) [39].

Exosomes and extracellular vesicles role in cancer detection

Exosomes, microvesicles, microparticles, oncosomes, apoptotic bodies, lipoprotein particles, and any other non-viral vesicle released or secreted by cells are all considered as extracellular vesicles [31].

Extracellular vesicles have a role in a wide range of physiological and pathological processes, including immunomodulatory responses, cancer metastasis, cell migration, proliferation, and intracellular communication. A cancerous cell's exosomes frequently exhibit the molecular makeup of the parent cell [31].

Exosomes have been demonstrated to be associated with angiogenesis, metastasis, immune response inhibition, and tumor growth. Biomarkers with proven clinical usefulness can be found using the nucleic acid cargo of extracellular vesicles and exosomes [31].

Exosomes are 40-100nm diameter endocytic vesicles that use at least three different processes to deliver information to the target cells, including proteins, DNA, mRNA, and noncoding RNAs: Receptor-ligand interaction, fusion with the plasma membrane, or phagocytosis-mediated endosytosis, Exosomal DNA may represent the mutational state of the parent tumor cells, as evidenced by the presence of dsDNA in tumor-derived exosomes [32].

Exosomes and the load they carry may be useful biomarkers for diagnosis, prognosis, and therapy response prediction. Exosomes from various cells under both normal and stressful setting have been identified and described [32]. There are numerous drawbacks to take into account, including the following: (i) tissue biopsies are invasive; (ii) certain tumor sites like the brain or lung are challenging to reach with a syringe: (iii) it is difficult or even impossible to perform sequential tissue biopsies on individual patients for real time monitoring of therapy response in clinical practice: (iv) intrapatient tumor heterogeneity may cause a single biopsy at tumor diagnosis to miss small but significant tumor clones; and (v) the process can take a long time [33].

Recent biomarkers

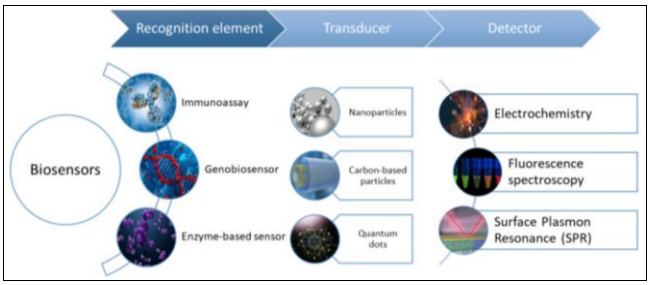

Fig 1: Different parts of the biosensors applicable in BC diagnosis: Recognition element, transducers, and detectors [28].

Table 5: Recent electrochemical sensors for BC biomarkers detection

Biomarker (Electrochemical sensors)	ELECTROCHEMICAL TECHNIQUE	biological sample	Reference
miR-21	FET	Urine	Mousazadeh *et al.* [28]
miR-21	DPV	Urine	D. Chen *et al.* [44]
NMP22	CV	Urine	D.Wu *et al.* [45]
NMP22	CV, DPV	Urine	Mousazadeh *et al.* [28]
NMP22	SWV,EIS	Urine	M. Li *et al.* [46]
NMP22	CV, DPV, EIS	Urine	S. Zhao *et al.* [47]
NMP22	Amperometry	Urine	S. Li *et al.* [48]
NMP22	SWV	Urine	Mousazadeh *et al.* [28]
NMP22	CV, EIS, DPV	Urine	M. Sharifuzzaman *et al.* [49]
NMP22	FET	Urine	Y. Yang *et al.* [50]
VOC	Resistance	Urine	Mousazadeh *et al.* [28]
IL-8	CV, DPV, EIS	Saliva	Mousazadeh *et al.* [28]

Conclusion

A global health concern is genitourinary (GU) malignancies, which include tumors of the prostate, kidneys, bladder and testicles. Although early detection is essential, conventional approaches are frequently instructive and have low accuracy, Non-invasive biomarkers that show promise for early diagnosis, monitoring, and tailored treatment include proteins (e.g.NMP22, BTA), DNA methylation, miRNAs, and exosomes. Although there are choices with FDA-approved tests like NMP22 and BTA, their low accuracy prevents broad adoption. In order to improve outcomes and lessen the burden of genitourinary malignancies, developments in biomarker research, multi-omics, and biosensors are opening the door to more accurate, efficient, and real-time diagnosis.

Conflicts of interest

There are no conflicts of interest.

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