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Approaches and Barriers to Biomarker Discovery: The Example of Biomarkers of Renal Scarring in Pediatric Urology 1

Ted Lee, Esther Finney, Anjali Jha, Anna Dorste, and Richard Lee

A noninvasive test that can longitudinally assess renal parenchymal status would be incredibly valuable for a wide range of conditions, including neurogenic bladder, renal transplantation, and upper and lower urinary tract anomalies. To address this need, enormous amounts of time, effort, and resources have been invested to identify biologic molecules that signal the pathologic processes of renal parenchymal defects. In this comprehensive narrative review, the authors summarize biomarkers that have previously been investigated while highlighting the key pitfalls and barriers that have impeded biomarker discovery and translation.

Biomarkers in Urolithiasis 19

David E. Hinojosa-Gonzalez and Brian H. Eisner

A variety of biomarkers have been studied in the setting of conditions and scenarios related to kidney stone disease. These biomarkers are commonly serum markers, novel urinary proteins, and inflammatory whose use is aimed at providing clinicians with additional information of underlying processes and improving detection and stratification of patients with kidney stones, acute ureteral obstruction, stone passage, and related infectious complications. Their adoption has been limited, and further evidence is required to determine their role in the care of patients with stone disease.

Biomarkers in Urethral Stricture Disease and Benign Lower Urinary Tract Disease 31

Jack G. Campbell, Joshua P. Hayden, and Alex J. Vanni

Increased understanding of molecular pathophysiology has led to the detection of clinically applicable biomarkers across medicine, which allow for minimally invasive detection, management, and monitoring of disease processes. Although biomarkers have traditionally played a more significant role in malignancy, these goals also pertain to benign disease. Herein, the authors review ongoing research into biomarker investigation and application in urethral stricture disease, benign prostatic hyperplasia, bladder outlet obstruction, and overactive bladder. No biomarkers for these entities are currently in clinical use; however, numerous physiologic pathways provide targets for current and future study.

Pathophysiology and Clinical Biomarkers in Interstitial Cystitis

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John M. Masterson, Peris R. Castañeda, and Jayoung Kim

Interstitial cystitis/bladder pain syndrome is a poorly understood yet prevalent condition accounting for a significant proportion of urology office visits. Identification of reliable biomarkers for disease remains an important yet challenging area of research given the heterogeneity of disease presentation and pathophysiology. A review of the literature by the authors revealed a handful of original investigations that revealed promising biomarkers within various physiologic processes or organ systems including immunity, inflammation, neural pathways, urothelial integrity, and anesthetic bladder capacity. Although no perfect biomarker has yet been identified for IC/BPS, research in this area has greatly expanded our understanding of disease.

Urine-Based Markers for Detection of Urothelial Cancer and for the Management of Non–Muscle-Invasive Bladder Cancer

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Yair Lotan and Fady J. Baky

Currently, evaluation for hematuria is driven by the AUA/SUFU guidelines, and urine markers are not recommended for routine evaluation. Bladder cancer is a disease characterized by a high recurrence rate that is impacted by stage and grade. The use of urine markers within the guidelines is recommended for very specific indications such as atypical cystoscopic findings or atypical cytologic findings. Routine use is also not recommended for patients undergoing surveillance. Many protein, DNA and RNA, and molecular biomarkers have been examined as an adjunct to cystoscopy and cytology in the diagnosis and surveillance of bladder cancer, and several FDA-approved tumor markers are now available. The role of biomarkers remains an important area of further study to enhance the diagnosis and surveillance of bladder cancer. Beyond this, tumor markers may also play an important role in risk stratification and prediction of treatment response, allowing for personalized care for patients with bladder cancer. This article reviews the urine biomarkers currently available in the diagnosis and surveillance of bladder cancer.

Biological Stratification of Invasive and Advanced Urothelial Carcinoma

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Moritz J. Reike, Alberto Contreras-Sanz, and Peter C. Black

Muscle-invasive urothelial carcinoma (UC) of the bladder remains a highly lethal malignancy. In this review the authors explore the underlying biology associated with the evolution from non–muscle-invasive UC to muscle-invasive and metastatic UC, with a special focus on the molecular stratification of UC and the potential of this stratification to be used for treatment selection.

The Association Between the Urinary Microbiome and Bladder Cancer

81

Ahmed A. Hussein, Gary Smith, and Khurshid A. Guru

Many studies are currently investigating the association between the urinary microbiome and bladder cancer, focusing on differences between stages and with risk of recurrence and progression. However, many of these studies are limited by the small number of patients, presence of confounders and issues with sampling, DNA extraction, and analyses. Recently there has been a shift toward examining the microbiome of bladder tissues rather than urine samples; however, these studies remain a minority. Identification of the differences in microbiome composition between different stages of bladder cancer can provide biomarkers to identify the patients who are more likely to respond to intravesical treatment. Further, these differences in microbiome composition could provide novel therapeutic targets, whereby the modulation of specific bacterial taxa could selectively promote or inhibit response to intravesical therapy.

Combined Use of Magnetic Resonance Imaging and Biomarker Testing to Detect Clinically Significant Prostate Cancer 91

Nathan L. Samora, Bashir Al Hussein Al Awamlh, and Jeffrey J. Tosoian

We performed a narrative review of studies that produced clinically applicable data by examining the combined use of at least one biomarker test and multiparametric MRI to predict GG ≥ 2 prostate cancer on biopsy and by reporting the resultant clinical outcomes (i.e, the proportion of biopsies avoided and GG ≥ 2 cancers missed) following the application of various testing strategies incorporating these diagnostic tests.

Circulating Tumor Cells and Circulating Tumor DNA in Urologic Cancers 109

Ikenna Madueke, Richard J. Lee, and David T. Miyamoto

Liquid biopsies such as circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) have great potential to serve as prognostic and predictive biomarkers in urologic cancers. The possibility of using liquid biopsies for real-time noninvasive and dynamic monitoring of response to therapy has been an active area of investigation. In this brief review, we outline the evidence for the potential clinical utility of CTC and ctDNA analyses in prostate, urothelial, and renal cancers.

Targeted Molecular Imaging as a Biomarker in Urologic Oncology 115

Arvin Haj-Mirzaian, Umar Mahmood, and Pedram Heidari

Urologic malignancies constitute a large portion of annually diagnosed cancers. Timely diagnosis, accurate staging, and assessment of tumor heterogeneity are essential to devising the best treatment strategy for individual patients. The high sensitivity of molecular imaging allows for early and sensitive detection of lesions that were not readily detectable using conventional imaging techniques. Moreover, molecular imaging enables the interrogation of molecular processes used in targeted cancer therapies and predicts cancer response to treatment. Here we review the current advancements in molecular imaging of urologic cancers, including prostatic, vesical, renal testicular, and ureteral cancers.

Biomarkers in Testicular Cancer: Classic Tumor Markers and Beyond 133

Jillian Egan and Keyan Salari

Biomarkers play a key role in patients with testicular germ cell tumors in a variety of clinical contexts, including initial diagnosis, prognostication, monitoring treatment response, and posttreatment surveillance. Although the classic serum tumor markers for testicular germ cell tumors are essential for clinical management, the low sensitivity (particularly for seminoma and teratoma) and potential for false positives has spurred novel biomarker discovery and validation efforts. Here, we review the current state of serum-based biomarkers for testicular germ cell tumors, with a focus on the classic serum tumor markers and emerging class of microRNA markers.

The Evolving Landscape of Viral, Immune, and Molecular Biomarkers in Penile Cancer 145

Alice Yu, Jad Chahoud, Andrea Necchi, and Philippe E. Spiess

Penile cancer is relatively rare in North America and Europe (<1% of all malignant neoplasms); however, it remains a significant health concern with a higher propensity of cases in many African, South American, and Asian countries. It occurs primarily in older men with a peak incidence in the 6th decade of life. The etiology of penile cancer is multifactorial and there are many risk factors including lack of neonatal circumcision, chronic inflammation, lichen sclerosis, tobacco use, obesity, poor

hygiene, exposure to ultraviolet radiation, history of sexually transmitted diseases, and human papillomavirus (HPV) infection. Pathogenesis of penile squamous cell carcinoma (PSCC) can be broadly dichotomized into HPV related and non-HPV-related pathways which will be discussed in detail in this review.

Current and Future Biomarkers in the Management of Renal Cell Carcinoma

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Stephen Reese, Lina Calderon, Sari Khaleel, and A. Ari Hakimi

Renal cell carcinoma biomarkers include serum, urine, liquid, and tissue biomarkers. There is currently an ongoing search for predictive biomarkers in the detection, recurrence, and treatment of renal cell carcinoma. Emerging signatures in the transcriptomic and translational biomarker space seem promising, although additional work is needed to validate candidates in a larger and more generalizable patient population.