

Urine: The Original Liquid Biopsy

Examination of the urine is considered one of the oldest forms of diagnostic testing. Detailed descriptions of urinary observations extend back to before the days of the Greek physician Hippocrates. From ancient times until the Victorian era, urine was used as the primary diagnostic tool with urine considered a “liquid window through which physicians could view the body’s inner workings”. How urine as a diagnostic tool evolved over the centuries gives some insight into how important it has become in the modern era of precision medicine. An overview of the history of urine in medicine has been summarized by Armstrong in his 2007 publication “Urinalysis in Western Culture: a brief summary”.¹

In ancient times, urine color (bloody, bilious), urine “bubbles” (proteinuria) and “sweetness” of the urine (diabetes) were simple urinary assessments. In the second century AD, Galen, a Greek physician in the Roman Empire, began to refine the practice of medicine. He identified that urine represented a filtrate of the blood and equated urine volume with states of health. Throughout the Middle Ages, visual evaluation of the urine attained new levels of diagnostic prominence that became known as “uroscopy”.

By the 17th century, “uromancy” was a term used to describe the exuberant and fanciful interpretation of urine to diagnose disease. Many practitioners of uroscopy, often with no medical training, would engage in the interpretation of a patient’s urine. A device known as a “piss pot” or matula, was a glass vessel that resembled the bladder with curved portions representing different parts of the body. The matula was used to collect and observe the urine with the “practitioners” findings based on their observations of color, consistency, sediment and odor. Reference charts were published to categorize urine. While some considered these practitioners to be legitimate, many individuals sought to discredit this as quackery. Uroscopy escaped medical control, becoming perhaps the first in home health test and often a tool of uneducated practitioners. In 1679, Thomas Brian published “The Pisse-Prophet”, a publication that ended the widespread practice of uroscopy.

For the next 250 years, advances in scientific methods and understanding of pathophysiology, chemistry, and microscopy allowed the study of urine to become legitimized. What have been the recent advances in the study of urine that have significantly impacted the practice of medicine in general and urology specifically? Some of the most prominent uses of urine today in urology involve the diagnosis of malignancy.

The urinary detection of urothelial carcinoma was well established in the 20th century. Urinary cytology could be used to detect malignancies from the upper tract through the urethra and became a standard of care. Starting with bladder cancer, the utility of urine as a diagnostic tool in urologic oncology began a new era in the 1990’s.

In the world of bladder cancer, numerous biomarkers debuted as diagnostic tests. A variety of ELISA, immunofluorescent, and other antigen detection methods based on urinary biomarkers came into the market. Advances in molecular detection continued into the 21st century with other biomarker advances relying on the use of PCR and the detection of a variety of mutated bladder cancer associated gene tests receiving FDA approval.² AUA guidelines for non-muscle invasive bladder cancer include recommendations for the use of these new biomarkers in specific clinical settings such as in the initial diagnosis of bladder cancer, in the use of specific markers to assess the response to intravesical therapy and in adjudicating equivocal cytology findings.

It is somewhat obvious that interrogation of the urine might help with the detection of urothelial malignancies. From the 1970’s through the early 1990’s, interest grew in metabolites, amino acids and other urinary factors including

urinary PSA that could be detected in men with prostate cancer. However, no reliable prostate cancer urinary assay was ever developed using these factors. In the late 1990's came the first suggestions that early prostate cancer may shed prostate cancer cells in the urine. The detection of early localized prostate cancer through the identification of shed cells completely changed the paradigm of using urine to aid in the diagnosis of prostate cancer. These molecular based early discoveries often relied on prostate massage to express cells. The identification of DD3 (also called PCA3) RNA, one of the first nucleic acid markers highly specific for prostate cancer, was the first approved urine specific marker to detect prostate cancer clinically.³ The observation that early prostate cancer could shed cells in the urine resulted in a rapid expansion of other prostate cancer urinary detection methods. Numerous urine tests are already approved for clinical use and many more are under study. The field has further expanded with specific urinary exosomes joining the ranks of urinary detection methods for prostate cancer. It should be noted that all of these markers are not diagnostic of prostate cancer but provide evidence that a definitive diagnostic prostate tissue biopsy should be performed.

Recently, renal cell carcinoma has been entered the field of urinary biomarkers. Beyond hematuria, a series of proteins, DNA methylation and micro RNA's are being explored as diagnostic urinary tools.

Most of the comments so far focus on the role of urine in the detection of urologic malignancies. This is not to minimize the utility of this amazing body fluid to evaluate the health status of an individual. Urine has the ability to provide precise information on many different body systems. My personal interest in detecting shed malignant cells was advanced by the 2020 book "Translational Urinomics" edited by Hugo Miguel Baptista Carreira dos Santo.⁴ This publication presents an overview of modern urinalysis using a variety of advanced laboratory techniques to investigate urine using transcriptomics, proteomics, metabolomics, lipidomics and others in a wide variety of diseases with many of these conditions outside of the urinary tract.

Urine has proven to be a source of sensitive markers that may be reflective of the earliest signs of diseases in the body. Intrinsic kidney diseases, hepatic diseases, urolithiasis, bone health, acute MI, systemic fluorosis (excess fluoride ingestion), unusual parasitic diseases, in addition to the genitourinary cancers noted previously, can be studied through urine samples. Basic urinalysis using microscopy and reagent dipsticks are common in everyday health care. PCR methods now allow rapid identification of urinary tract infectious agents and can provide antibiotic sensitivities without the need for cultures.

Currently there is great interest in precision medicine through the use of "liquid biopsies" in a wide variety of malignancies. Precision medicine can improve patient management by guiding therapeutic decisions based on specific patient disease characteristics, many of which can now be identified in the urine. It seems urine should be credited as the original and all-natural liquid biopsy.

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