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In This Issue:

Recent advancements in POCTs and significance of AI/ML for detection of Drug-induced Nephrotoxicity and Therapeutic Drug Monitoring

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From preventive healthcare to predictive healthcare, we have come a long way. Today, the healthcare industry is emerging rapidly and delivering effective and patient-centered services; however, under-developed and developing economies are still struggling owing to shortage of hospitals, experienced doctors, faster diagnosis, advanced laboratory tests and skilled staff. While conventional laboratory techniques remain the cornerstone of diagnostic testing, point-of-care testing (POCT) has emerged in recent times to meet several pressing demands and current challenges faced by the healthcare sector. Although specificity and sensitivity are better with standard laboratory testing compared to POCTs, such lab set ups are absent in remote areas. In the dearth of advanced lab setups, delayed testing holds up timely diagnosis and accurate clinical decision making. On the other hand, by bringing diagnostic testing closer to the subjects and in the real-world, POCTs have re-shaped the face of today's healthcare. Additionally, the ease of performing these tests with non-invasive biological samples such as urine, serum, saliva, plasma, stool for early detection of the diseases has been quite fruitful and convenient. As per the data from Pan American Health Organization (PAHO), chronic kidney diseases (CKD), including acute glomerulonephritis and CKD due to diabetes (CKDD) are ranked as the 8th cause of mortality and disease burden in the region of America in 2019 (1). Rapid and accurate diagnosis

and timely intervention can help in preventing severe kidney damage and ensuring better patient outcomes. Currently, commonly used POC devices are used in low-resource settings for creatinine testing to check the prevalence of CKD of non-traditional origin (CKDnt) (2). Nephrotoxicity or the rapid deterioration in the kidney function due to toxic effect of medications or conditions like renal tubular toxicity, inflammation, glomerular damage, crystal nephropathy, and thrombotic microangiopathy are assessed as part of therapeutic drug monitoring (TDM). Interestingly, about 26% of nephrotoxic cases are drug-induced (3, 4) and testing of these cases is done by various assays which measure biomarkers like serum creatinine, blood urea nitrogen (BUN), urine albumin, cystatin C, kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and clusterin (5). Moreover, eGFR (estimated glomerular filtration rate) is another reliable test for doctors to know how well the kidneys are functioning. In this article, the authors have highlighted the importance of how urinalysis is crucial for early screening in renal healthcare, nephrotoxicity detection, monitoring assays/kits and what crucial role POCTs and advanced technologies like artificial intelligence/machine learning (AI/ML) are playing in this therapeutic area to further augment the timely diagnosis.

Urinalysis is a potential diagnostic tool that provides comprehensive insights into kidney function, metabolic status, urinary tract infections and potential toxicity, by assessing parameters such as pH, protein, glucose, ketones, bilirubin and leukocytes. Furthermore, urinalysis involves examining the microscopic, physical and chemical properties of urine to detect oddities with methods like urine dipstick testing, lateral flow assays (LFA), microscopy, advanced POCTs like urine analyzers and microfluidic paper-based analytical devices (µPADs) (5). As per FDA released Drug-Induced Renal Injury List (DIRIL) dataset, the list consists of single-molecule, oral administered drugs for human use, annotated for DIRI and nephrotoxicity. We sieved this information and prepared Table 1 consisting of all the drugs conferring nephrotoxicity. We further downloaded the list of OTC kits/assays and their manufacturers available for top 10 drugs of abuse (Figure 2).

Undoubtedly, laboratory tests provide rapid qualitative or semi-quantitative results, aiding in the diagnosis of various conditions like urinary tract infections, renal disorders, and metabolic abnormalities whereas the POCTs in general face challenges of low sensitivity, high cross-reactivity, low reproducibility, false positives and negatives (5,6). However, based on recent research studies, next-generation POCTs like paper-based microfluidics score better compared to their predecessors (7). Recently, several cutting-edge analytical concepts and devices are evolving and upgrading the POCT spectrum in renal healthcare. Remote digital urinalysis is now coupled with smart phones to facilitate online counseling, remote diagnostics, and real-time data transmission, which means POCTs in remote settings can now complement the advanced kidney function tests (8). The wearable biosensor for clinical application is another upcoming technology

to facilitate continuous tracking of a patient's health status. Data about vitals, the concentration of biomarkers, and disease progression in real time can easily be transmitted by implantable biosensors like urinary catheters, intraocular pressure, and glucose sensors (7).

Further advancements in POCTs, coupled with AI, are revolutionizing healthcare by enhancing the speed, accuracy, and efficiency of diagnostic testing by introducing AI-based applications like image recognition in urine microscopy in which AI-based image recognition algorithms can discern and measure cellular and non-cellular components, including casts, crystals, red and white blood cells, in microscopic images of urine sediment (10, 11). With great precision and accuracy, these algorithms can identify and categorize the constituents of urine sediment, offering important diagnostic data for kidney disorders, urinary tract infections, and renal functions. To provide clinicians with real-time decision support, AI algorithms like decision support systems (DSS) for interpretations may examine intricate patterns and correlations found in urine test results (10, 11). Such AI-driven DSS help healthcare providers interpret results, guide diagnosis with better treatment decisions, and forecast patient outcomes by combining patient data, medical history, and laboratory results. Additionally, predictive modeling can also support early disease prediction, identify high-risk individuals, and optimize treatment plans by utilizing data from wearables, electronic health records (EHRs), POCT devices, and other sources. AI-based predictive analytics in the context of urinalysis can predict the onset of kidney illnesses, UTIs, and other urinary problems, allowing for preemptive intervention and individualized treatment strategies. With advancements in technologies, continuum care healthcare models are being adopted globally with personalized treatment optimization which includes comprehensive archives of POCT findings, other relevant historical data, demographic information, and clinical outcomes that can be analyzed by AI algorithms to find individualized treatment plans and enhance therapeutic outcomes. AI-driven treatment algorithms can project treatment responses, refine treatment plans, and personalized medicine dosages based on patient features, genetics, and biomarker profiles, all of which contribute to improved patient outcomes. The AI-enabled POCT devices can be integrated with telemedicine applications and remote monitoring systems. The amalgamation of AI and credible, cost-effective POCT technologies has enormous potential to revolutionize renal healthcare delivery through enhanced patient outcomes, treatment strategy optimization, and improved first-hand diagnosis accuracy in urinalysis and beyond.

While AI offers rapid and precise diagnostics to improve POCT landscape, it is not intended to substitute conventional laboratory tests. AI based models need to be refined for accuracy and error minimization, that depends on large-scale datasets for training the AI models. AI speeds up preliminary screenings, but conventional lab methods are still necessary for in-depth examinations, specialized testing and important source of reference data in training AI/ML models. Therefore, the beneficial relationship between AI and conventional techniques

guarantees effective and dependable POCT processes not only for renal healthcare advancements but in general for better disease prognosis and prevention.

References:

1) PAHO. The burden of kidney diseases in the Region of the Americas, 2000-2019. Pan American Health Organization. 2021.

2) Dally M, 2023; Point-of-Care Testing in Chronic Kidney Disease of Non-Traditional Origin: Considerations for Clinical, Epidemiological, and Health Surveillance Research and Practice. Ann Glob Health. Feb 1;89(1):7

3) Skylar Connor; 2024; Generation of a drug induced renal injury list to facilitate the development of new approach methodologies for nephrotoxicity, Drug Discovery Today, 29:4

4) Perazella MA; 2018; Pharmacology behind Common Drug Nephrotoxicities. Clinical J Am Soc Nephrol;13, 1897-1908.

5) Lei R, Huo R, Mohan C. Current and emerging trends in point-of-care urinalysis tests. Expert Rev Mol Diagn. 2020

6) Can we trust urine dipsticks? | *Sykepleien* [Internet]. [cited 2019 Jul 26]. Available from: https://sykepleien.no/en/forskning/2017/01/can-we-trust-urine-dipsticks

7) Hwang C;2022; Recent Advances in Biosensor Technologies for Point-of-Care Urinalysis. Biosensors (Basel).12(11):1020.

8) Stauss M; 2021; Remote digital urinalysis with smartphone technology as part of remote management of glomerular disease during the SARS-CoV-2 virus pandemic: single-centre experience in 25 patients. Clin Kidney J;1;15(5):903-911.

9) Khan AI; 2023; Artificial Intelligence in Point-of-Care Testing. Annals of Laboratory Medicine Sep 1; 43(5):401-407.

10) Sander De Bruyne; 2023; Applications of Artificial Intelligence in Urinalysis: Is the Future Already Here? *Clinical Chemistry*, 69:12,

11) Campos-Medina; 2024; J.A. AI-Enhanced Blood Cell Recognition and Analysis: Advancing Traditional Microscopy with the Web-Based Platform IKOSA. *Journal of Molecular Pathology.*, *5*.

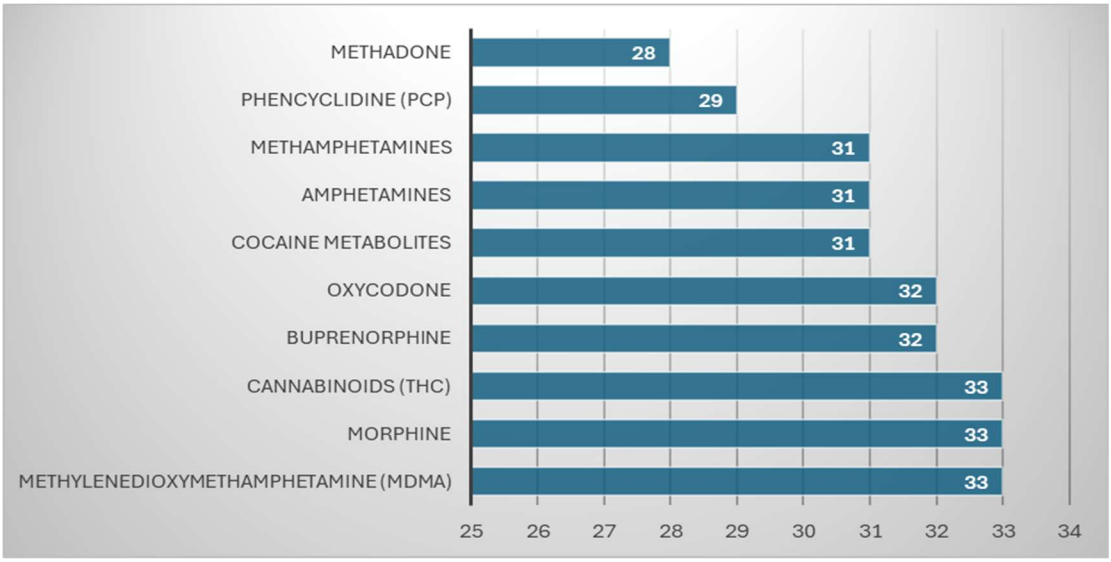
Tables & Figures

Table 1: Details of the drugs implicated in causing drug toxicity/nephrotoxicity (as per the FDA DIRIL database for drug toxicity/nephrotoxicity)

PubChem_CID	Drugbank_id	Name	Product_country	Toxicity
10184653	DB08916	Afatinib	Canada|EU|US	Nephrotoxic
3672	DB01050	Ibuprofen	Canada|EU|US	Nephrotoxic
5291	DB00619	Imatinib	Canada|EU|US	Nephrotoxic
134780	DB08910	Pomalidomide	Canada|EU|US	Nephrotoxic
216239	DB00398	Sorafenib	Canada|EU|US	Nephrotoxic
60846	DB00177	Valsartan	Canada|EU|US	Nephrotoxic
71616	DB00582	Voriconazole	Canada|EU|US	Nephrotoxic
35370	DB00495	Zidovudine	Canada|EU|US	Nephrotoxic
2764	DB00537	Ciprofloxacin	Canada|US	Nephrotoxic
2907	DB00531	Cyclophosphamide	Canada|US	Nephrotoxic
60852	DB00710	Ibandronate	Canada|EU|US	Nephrotoxic
64929	DB13873	Fenofibric acid	US	Nephrotoxic

PubChem_CID	Drugbank_id	Name	Product_country	Toxicity
5284627	DB00273	Topiramate	Canada|US	Nephrotoxic
5734	DB00909	Zonisamide	EU|US	Nephrotoxic
3034010	DB01083	Orlistat	Canada|EU|US	Nephrotoxic
4075	DB00244	Mesalazine	Canada|US	Nephrotoxic
4594	DB00338	Omeprazole	Canada|US	Nephrotoxic
3637	DB01275	Hydralazine	Canada|US	Nephrotoxic
60871	DB00718	Adefovir dipivoxil	Canada|EU|US	Nephrotoxic
44462760	DB08912	Dabrafenib	Canada|EU|US	Nephrotoxic
11707110	DB08911	Trametinib	Canada|EU|US	Nephrotoxic
14969	DB00512	Vancomycin	Canada|US	Nephrotoxic

Figure 2: Top 10 drugs with the number of OTC kits/assays available from various manufacturers. The numbers (mentioned on X-axis) indicate different manufactures for the drug (mentioned on Y axis). Source: FDA dataset



Editor's Corner:

Dear TDM/Toxicology Division Members:
It is exciting time for our division as well as TDM. As you know, all ADLM Scientific Divisions have been reorganized and consolidated. In TDM, a plethora of exciting drugs have been released, and more are in development. Two exciting areas of new drugs are humanized monoclonal antibodies and antibody-drug conjugates. Another new class of drugs exploit the cells' ability to 'poison' genetic transcripts, either to decrease mutated proteins or to enhance desired proteins. One analysis found that the human genome could contain 1.6 million poison exons. This will surely be a new potential avenue of drug development.
-Pradip Datta, editor.

We need your ideas and article contributions for this newsletter. It is a good opportunity to put authorship in resume. Please contact Pradip Datta, Newsletter editor at p.datta581@gmail.com.

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