Kidney Medicine

Nephrology Lagging Behind in Machine Learning Utilization

Clarissa Cassol and Shree Sharma

In this issue of *Kidney Medicine*, Verma et al[1] highlight the underuse of machine learning as a research tool in the field of nephrology. Through a bibliometric search approach, they found that kidney research had the lowest

Related article, p. 762

number of articles using machine learning when compared with 4 other organ-specific research areas (brain, heart, liver, and lung). Additionally, among machine learning articles, the National Institute of Diabetes and Digestive and Kidney Diseases had the lowest number of acknowledgements as a funding source compared with 7 other National Institutes of Health institution sponsors. Organ-specific specialty journals were also found to have fewer articles featuring machine learning when compared with broad interdisciplinary journals. These findings highlight the importance of educating the nephrology community about the potential advantages (as well as inherent limitations) of artificial intelligence (AI) research tools.

Although the scarcity of publications within the nephrology field using machine learning has already been pointed out,[2,3] Verma et al[1] rigorously document this finding while also placing this into perspective with other organ-specific fields and highlighting the disparity of funding specifically directed toward machine learning research within nephrology. The article is very timely because of the increasing number of clinical trials and rapid advancement in the field of diagnostics and therapeutics, areas that might get a further boost with the integration of machine learning.

AI refers to the development of algorithms that allow a computer to perceive, learn from data, react, make predictions, and act.[4] Machine learning is one of the branches of AI and comprises a set of algorithms, such as convoluted neural networks, random forest, and deep learning, that have the ability to learn and improve from experience without having been explicitly programmed for a specific task.[4] Convoluted neural networks are particularly efficient at analyzing data that are spatially or temporally dependent, such as images, explaining their popularity in radiology and pathology machine learning reseach.[5]

One of the advantages of deep learning is its ability to analyze big and complex data and yield predictions that in general tend to be similar to or outperform human experts. Humans become "expert" in their fields over many years after gathering and analyzing millions of data points in their brains. The number of data points that can be analyzed by machine learning is huge, and machine learning has a clear speed advantage over humans, offering the potential of advancing our understanding much faster.

The requirement of a substantial amount of data for training of convoluted neural networks can be a limiting factor when dealing with rare diseases, as is the case with glomerular diseases for instance.[4] The creation of large consortiums, such as the Nephrotic Syndrome Study Network (NEPTUNE), the Kidney Precision Medicine Project (KPMP), the Chronic Renal Insufficiency Cohort (CRIC), and the Cure Glomerulonephritis (CureGN) Study, is a potential way to circumvent this issue.[4] Data obtained through these consortiums have already been used in machine learning research. For instance, digitalized kidney pathology slides from the NEPTUNE database have been used to train a convoluted neural network to segment normal kidney histologic structures, including glomeruli, distal and proximal tubules, and peritubular capillaries.[6] The assessment of pathologic features, such as interstitial fibrosis and tubular atrophy, has also been the subject of machine learning studies,[7] including for prediction of kidney survival.[8] Other pathologic states for which convoluted neural networks have been successfully trained to grade and classify include diabetic nephropathy,[9] lupus nephritis,[10] and interpretation of immunofluorescence images.[11]

In another example of how large disease consortiums could facilitate future machine learning research, data from the KPMP database are being used to generate and feed ontologies that could be used on AI/machine learning projects to link various -omics profiles to clinical features.[12] One of the major advantages of the consortiums is the annotation and review of the digital images by experts from all over the world. The annotated images help provide the ground truth for the development of supervised AI algorithms. After validation of the algorithms, these annotated images can be made available in the public domain to help individual institutes develop their own algorithms. In most studies, the κ for kidney pathology parameters is very high. Machine learning and open-sourced reviewed annotated images may help improve the reproducibility of the findings and patient outcomes.

Given their ability to analyze and integrate large amounts of complex data, machine learning tools are ideal to facilitate understanding of genotype-phenotype relationships in kidney diseases, which requires integration of digital nephropathology and radiology, transcriptomics, proteomics, metabolomics, and genome sequencing, as well as other data modalities such as electronic health record repositories.[13] Within the transplant field, one promising initiative is the creation of the Banff Digital Pathology Working Group,[14] which should increase the availability and use of whole slide images of kidney transplant biopsies for future use in AI/machine learning research. Future potential applications of AI//machine learning in nephropathology include the assessment of transplant donor biopsies[15] that are often read by non-nephropathologists with limited expertise in medical renal pathology, 3-dimensional reconstruction of kidney biopsy tissue,[16] and smartphone-based technologies to assist with adequacy evaluation of kidney core biopsies in real time, among others (reviewed by Huo et al[16]).

A few examples of nephrology-specific AI applications include prediction of the development of left ventricular dysfunction in patients with chronic kidney disease (CKD),[17] risk for developing progressive immunoglobulin A nephropathy,[18] dry weight assessment in maintenance dialysis patients,[19] acute kidney injury prediction in inpatients[20] including in the intensive care unit setting,[21] identification of pathogen-specific immune fingerprints in peritoneal dialysis patients,[22] and even noninvasive high potassium detection through deep learning of electrocardiogram (ECG) patterns on a smartwatch.[23,24] Similar smartphone-based technology has also been used to detect atrial fibrillation, and it is currently US Food and Drug Administration (FDA) approved.[25] A database of FDA-approved health care AI applications[26] includes 36 applications in radiology, 16 in cardiology, 6 in internal medicine, 5 in neurology, 3 in ophthalmology, 2 each in endocrinology and psychiatry, and 1 in pathology and urology,[26,27] again highlighting the paucity of nephrology-specific AI research leading to the development of clinical applications. The single urology-related FDA-approved AI application consists of a smartphone-based urinalysis test kit to be used for at-home diagnosis of urinary tract infections.[28]

Given the extensive interface between kidney and cardiovascular diseases, many AI approaches that are currently being considered for patients with cardiovascular diseases could also prove useful among the kidney patient community. These include the use of wearable devices to detect hemodynamic changes, including blood pressure levels through photoplethysmography, biomechanical sensors incorporated into clothing or shoes that could continuously measure cardiac output, lung fluid volume and weight, and tattoo-like sensors based on microfluidics for continuous hemodynamic monitoring.[29,30]

Due to the similarities between the retinal and kidney microcirculation, retinopathy has been proposed as a noninvasive biomarker of microvascular disorders in patients with CKD.[31] Machine learning–based algorithms have been developed to assist in the diagnosis and classification of diabetic retinopathy[32]; a similar algorithm could be tested in retinal images from patients with CKD to assist in disease severity stratification, risk for CKD progression,[33] or the development of cardiovascular disease.[34]

However, all these promising potential clinical applications can only reach the bedside after extensive research and validation, for which funding and motivation from the nephrology community to pursue those studies are essential. In this regard, Verma et al's findings could be used to advocate for increased support from funding agencies into AI/machine learning–based kidney research. As suggested by Verma et al,[1] strategies to increase awareness and interest of nephrologists regarding machine learning could include introducing AI machine learning applications early in medical training to increase future physicians' familiarity with these tools. One such successful example includes the integration of an iPad-based ECG platform into preclerkship physiology teaching of first-year medical students at the University of California, Irvine School of Medicine.[35] The same platform is also FDA approved to record, store, and transfer single-channel ECG rhythms.

Currently, machine learning is not an integral part of nephrology fellowship or internal medicine training curriculum. Physicians are not trained to use this technology in practice. The current path for AI/machine learning applications is that 2 people interested in technology will talk and will come up with projects of mutual interest. Nephrology can do better than this. To expedite the development of this field, we need to include machine learning curriculum in training and develop more collaborative opportunities. Another initiative that should improve the nephrology community awareness and understanding of AI and machine learning tools is a recent review series published by a leading kidney specialty journal,[2] as well as the incorporation of AI/machine learning sessions in nephrology meetings such as the American Society of Nephrology Kidney Week and the International Society of Nephrology. Critically, Verma et al highlight the gap between nephrology and other organ-based research using AI/machine learning, calling attention to a field that can help improve health moving forward if this gap is addressed.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Clarissa Cassol, MD and Shree Sharma, MD.

Authors' Affiliation: Arkana Laboratories, Little Rock, AR.

Address for Correspondence: Clarissa Cassol, Arkana Laboratories, 10810 Executive Center Dr, Ste 100 Little Rock, AR 72211. Email: clarissa.cassol@arkanalabs.com

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received August 18, 2021, in response to an invitation from the journal. Direct editorial input from the Editor-in-Chief. Accepted in revised form August 20, 2021.

 Published online August 26, 2021 with doi 10.1016/j.xkme.2021.08.004

REFERENCES

1. Verma A, Vipul CC, Waikar SS, Kolachalama VB. Machine learning applications in nephrology: a bibliometric analysis comparing kidney studies to other medicine subspecialities. *Kidney Med*. 2021;3(5):762-767.
2. Chan L, Vaid A, Nadkarni GN. Applications of machine learning methods in kidney disease: hope or hype? *Curr Opin Nephrol Hypertens*. 2020;29(3):319-326.
3. Saez-Rodriguez J, Rinschen MM, Floege J, Kramann R. Big science and big data in nephrology. *Kidney Int*. 2019;95(6):1326-1337.
4. Niel O, Bastard P. Artificial intelligence in nephrology: core concepts, clinical applications, and perspectives. *Am J Kidney Dis*. 2019;74(6):803-810.
5. Liu Y, Chen PC, Krause J, Peng L. How to read articles that use machine learning: users' guides to the medical literature. *JAMA*. 2019;322(18):1806-1816.
6. Jayapandian CP, Chen Y, Janowczyk AR, et al. Development and evaluation of deep learning-based segmentation of histologic structures in the kidney cortex with multiple histologic stains. *Kidney Int*. 2021;99(1):86-101.
7. Ginley B, Jen KY, Han SS, et al. Automated computational detection of interstitial fibrosis, tubular atrophy, and glomerulosclerosis. *J Am Soc Nephrol*. 2021;32(4):837-850.
8. Kolachalama VB, Singh P, Lin CQ, et al. Association of pathological fibrosis with renal survival using deep neural networks. *Kidney Int Rep*. 2018;3(2):464-475.
9. Ginley B, Lutnick B, Jen KY, et al. Computational segmentation and classification of diabetic glomerulosclerosis. *J Am Soc Nephrol*. 2019;30(10):1953-1967.
10. Ginley B, Jen K-Y, Rosenberg A, et al. Fully automated classification of glomerular lesions in lupus nephritis. Paper presented at: SPIE Medical Imaging. March 16, 2020; Houston, TX. Proc. SPIE 11320, Medical Imaging 2020: Digital Pathology, 113200Y.
11. Ligabue G, Pollastri F, Fontana F, et al. Evaluation of the classification accuracy of the kidney biopsy direct immunofluorescence through convolutional neural networks. *Clin J Am Soc Nephrol*. 2020;15(10):1445-1454.
12. Ong E, Wang LL, Schaub J, et al. Modelling kidney disease using ontology: insights from the Kidney Precision Medicine Project. *Nat Rev Nephrol*. 2020;16(11):686-696.
13. Sealfon RSG, Mariani LH, Kretzler M, Troyanskaya OG. Machine learning, the kidney, and genotype-phenotype analysis. *Kidney Int*. 2020;97(6):1141-1149.
14. Farris AB, Moghe I, Wu S, et al. Banff Digital Pathology Working Group: Going digital in transplant pathology. *Am J Transplant*. 2020;20(9):2392-2399.
15. Marsh JN, Matlock MK, Kudose S, et al. Deep learning global glomerulosclerosis in transplant kidney frozen sections. *IEEE Trans Med Imaging*. 2018;37(12):2718-2728.
16. Huo Y, Deng R, Liu Q, Fogo AB, Yang H. AI applications in renal pathology. *Kidney Int*. 2021;99(6):1309-1320.
17. Attia ZI, Kapa S, Lopez-Jimenez F, et al. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat Med*. 2019;25(1):70-74.
18. Geddes CC, Fox JG, Allison ME, Boulton-Jones JM, Simpson K. An artificial neural network can select patients at high risk of developing progressive IgA nephropathy more accurately than experienced nephrologists. *Nephrol Dial Transplant*. 1998;13(1):67-71.
19. Niel O, Bastard P, Boussard C, Hogan J, Kwon T, Deschenes G. Artificial intelligence outperforms experienced nephrologists to assess dry weight in pediatric patients on chronic hemodialysis. *Pediatr Nephrol*. 2018;33(10):1799-1803.
20. Tomasev N, Glorot X, Rae JW, et al. A clinically applicable approach to continuous prediction of future acute kidney injury. *Nature*. 2019;572(7767):116-119.
21. Le S, Allen A, Calvert J, et al. Convolutional neural network model for intensive care unit acute kidney injury prediction. *Kidney Int Rep*. 2021;6(5):1289-1298.
22. Zhang J, Friberg IM, Kift-Morgan A, et al. Machine-learning algorithms define pathogen-specific local immune fingerprints in peritoneal dialysis patients with bacterial infections. *Kidney Int*. 2017;92(1):179-191.
23. Galloway CD, Valys AV, Petterson FL, et al. Non-invasive detection of hyperkalemia with a smartphone electrocardiogram and artificial intelligence [abstract]. *J Am Coll Cardiol*. 2018;71(11)(suppl):A272.
24. Galloway CD, Valys AV, Shreibati JB, et al. Development and validation of a deep-learning model to screen for hyperkalemia from the electrocardiogram. *JAMA Cardiol*. 2019;4(5):428-436.
25. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med*. 2019;25(1):44-56.
26. Benjamens S, Dhunnoo P, Meskó B. The state of artificial intelligence-based FDA-approved medical devices and algorithms: an online database. *NPJ Digital Med*. 2020;3:118.
27. FDA-approved A. I.-based algorithms. Accessed July 6, 2021. https://medicalfuturist.com/fda-approved-ai-based-algorithms/
28. Peck AD. FDA approves smartphone-based urinalysis test kit for at-home use that matches quality of clinical laboratory tests. Laboratory Pathology Web site. Published 2019. Accessed July 6, 2021. https://www.darkdaily.com/2019/03/06/fda-approves-smartphone-based-urinalysis-test-kit-for-at-home-use-that-matches-quality-of-clinical-laboratory-tests/
29. Bayoumy K, Gaber M, Elshafeey A, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. *Nat Rev Cardiol*. 2021:1-19.
30. Krittanawong C, Rogers AJ, Johnson KW, et al. Integration of novel monitoring devices with machine learning technology for scalable cardiovascular management. *Nat Rev Cardiol*. 2021;18(2):75-91.
31. Farrah TE, Dhillon B, Keane PA, Webb DJ, Dhaun N. The eye, the kidney, and cardiovascular disease: old concepts, better tools, and new horizons. *Kidney Int*. 2020;98(2):323-342.
32. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA*. 2016;316(22):2402-2410.
33. Grunwald JE, Pistilli M, Ying GS, et al. Association between progression of retinopathy and concurrent progression of kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *JAMA Ophthalmol*. 2019;137(7):767-774.
34. Grunwald JE, Pistilli M, Ying GS, et al. Progression of retinopathy and incidence of cardiovascular disease: findings from the Chronic Renal Insufficiency Cohort Study. *Br J Ophthalmol*. 2021;105(2):246-252.
35. Frisch EH, Greb AC, Youm JH, Wiechmann WF, Greenberg ML. Illustrating clinical relevance in the preclerkship medical school curriculum through active learning with KardiaMobile electrocardiography. *Adv Physiol Educ*. 2021;45(1):48-52.