Commentary: The Digital Fate of Glomeruli in Renal Biopsy

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We read with interest the recently published paper of Wilbur *et al*. on the development of a machine learning algorithm able to recognize and count glomeruli in renal biopsies with a simultaneous comparison of four stains.[1] The authors developed a prototype system able to display synchronized sections and detect features with a machine learning-based approach in medical renal biopsies. The algorithm is able to automate the detection of glomeruli, displayed in four stains (hematoxylin and eosin [H and E], silver, trichrome, periodic acid Schiff [PAS]) as the digital slides could be moved simultaneously in four screens, and the glomeruli are identified in a synchronized fashion. To achieve this, a preliminary phase of image registration was necessary. This consisted in the translation of any point on one registered whole slide image (WSI) to a corresponding point on the other registered WSI with the aid of so-called key-points (e.g., corners and appendages of tissue in the slide). This allowed displaying of the registered serial sections of the tissue in a 4-panel viewer in which each stain is visualized in its own area. The navigation of each panel is synchronized for both movement and magnification. Subsequently, pathologists annotate manually the glomeruli and the model is trained and then tested to detect glomeruli in two different slide sets. They reported a significant efficiency advantage over standard single slide microscopic review and the ability to directly compare staining features simultaneously on each glomerulus, as well as the ability to auto-locate a high majority (>90%) of all glomeruli present in each specimen. This could lead to a more accurate final interpretation through improved correlation of findings.[1] The paper has offered the chance to discuss some interesting points about the specific topic of glomeruli detection and assessment in kidney biopsy which go beyond the specific technical features of the developed algorithm itself.

Nephropathology is a niche field of pathology which refers to many different scenarios: Renal biopsies are taken for primary diagnosis of kidney diseases, for assessment of rejection in recipients of a kidney transplant, and also before transplant procedure to decide on kidney organ suitability to be transplanted. Furthermore, many systemic diseases such as diabetes and amyloidosis can show renal involvement which can be superimposed to the primary disease, and many medications for immune disease or for prevention of rejection can lead to renal damage. Morphological alterations of renal functional tissue are described with many histological elementary lesions affecting glomeruli and their components, different types of tubules, and the vascular compartment, which are often subtle and require ancillary techniques and specific training for detection, quantification, and correlation with clinical data, ultimately leading to diagnosis. Despite so numerous and critical settings, expertise in renal pathology is rare nowadays and a shortage of pathologists with specific training in the field is an issue. Concerning renal biopsy for primary diagnosis of glomerulopathies and similarly for rejection evaluation, the pathologist has to evaluate subtle alterations of glomerular, tubular, and vascular structures, with the aid of additional stains, immunohistochemistry of several markers of rejection or damage, immunofluorescence technique with also the possibility of multiplex staining,[2,3] and electron microscopy. However, nephropathology services are usually available at larger institutions only because of the special equipment/techniques, the low number of biopsies processed compared to other fields, and the special expertise needed to manage the cases.[4] Almost the same applies to posttransplant kidney biopsy: detailed criteria for biopsy assessment have been established such as the Banff criteria and require specific training and expertise.[5,6] Moreover, posttransplant renal pathology deals not only with the evaluation of rejection but also with posttransplant functional alterations whose morphological correlation on histology greatly overlaps with primary nephropathy diagnosis in terms of time-consuming assessment of biopsy with many different ancillary techniques.[7,8] The glomerular compartment is often the most affected in kidney functional tissue and despite increasing research in soluble and molecular markers of disease, kidney biopsy remains the gold standard for many glomerulopathies.[9-11] Some different considerations concern the evaluation of preimplantation kidney biopsy. At the opposite of renal biopsy for primary diagnosis or posttransplant follow-up, these biopsies are usually performed in an urgency setting where an on-call pathologist with no specific expertise has to evaluate the adequacy of biopsy and presence and widespread of glomerular damage in terms of percentage of sclerotic glomeruli to guide suitability and allocation or discard of the organ.[12-14] Usually, no ancillary staining is available due to the short turn-around-time requested and the pathologist may be forced to evaluate the biopsy with a frozen section. Moreover, glomerulosclerosis is recognized as the main feature leading to organ discard and with conflicting evidence on the impact on the graft outcome in case of transplantation.[15,16] Even for glomerulosclerosis evaluation in the preimplantation biopsy, expertise of reading pathologist plays a critical role, with expert pathologists more reproducible and reliable than general pathologists.[17-19] However, both in primary diagnosis or posttransplant or preimplantation biopsy, glomerular assessment starts with identification and enumeration of glomeruli in the biopsy: despite a seemingly simple task, the poor reproducibility among pathologists and the shortage of expert pathologists rises the demand for technological aid.

Digital pathology with WSI has shown to be reliable for routine surgical pathology diagnosis,[20,21] and also with frozen section[22,23] and cytopathology specimens.[24] Digital pathology has also been employed successfully for second-opinion consultations and expert reviewing,[25-27] case archiving and retrieval, teaching, and academic research, but, as briefly mentioned also by the authors, adoption remains slow because of the cost of equipment and the practical value to users which is still perceived as limited and day to day primary interpretation still lags behind standard microscopy for efficiency.[1] Artificial intelligence (AI) with machine learning techniques are being increasingly employed in WSI slides with H and E with pathology-centric approaches for tumor region identification, detection of metastatic foci, tumor classification, and prediction of gene mutations. As such, AI techniques promise to provide pathologists with a number of useful tools, beginning with mechanisms for automated case review and eventually leading to computer-aided diagnosis, thus undoubtedly enhancing pathology workflows and ultimately improving patient outcomes.[28] Glomerular identification, counting, and sorting as sclerosed or not sclerosed or with otherwise specified signs of damage represent a perfect example of a task for such machine learning algorithms and computer-aided diagnosis: indeed, the task itself is repetitive and glomerular structures in suboptimal slides could be challenging to identify for not trained pathologists. Interest in the application of digital pathology with image analysis algorithms to kidney biopsy is constantly growing, with sparse published experiences, particularly in transplantation.[29] While most of the studies applying automated algorithms to renal biopsy mainly deal with quantification of rejection related inflammatory elements or interstitial fibrosis,[30-32] studies focusing specifically on glomeruli have started to be published, both for transplant biopsies,[33,34] primary disease[35] and animal model of the disease.[36] Marsh *et al*. focused on the detection of glomeruli and sorting in sclerosed versus normal in frozen sections of preimplantation biopsies. They compared a conventional patch-based convolutional neural network (CNN) model with a fully convolutional CNN model and showed that the performance of the fully convolutional CNN model in terms of speed and accuracy is superior and can be quickly trained on a relatively small dataset to yield results on par with expert renal pathologist interpretation.[33] Kannan *et al*. found a 93% accuracy for detection of glomeruli in cropped digital images of trichrome stains in human renal biopsies with CNN and a segmentation model.[35] Hermsen *et al*. trained a CNN for the tasks of detection and segmentation of glomeruli both sclerosed and normal and of different types of renal tubules on kidney biopsies and whole specimens of two institutions stained with PAS, obtaining a 97% accuracy. The authors stressed the importance of the applicability of the algorithm to slides stained, processed, and scanned at different institutions, thus recognizing the value and the potential implications for teleconsultation and expert review.[34] This point concerning applicability to different stains and the high comparability with the expert review is stressed also in the work of Wilbur *et al*., that critically discusses the limitation of their study, as they recognize that pathologists involved in manual annotation where of the mixed level of expertise and that the cases were from the same institution. They are however right in highlighting that they were the first to apply a CNN model simultaneously to four stains, and they are fully aware of the issues related to diagnostic performance parameters (sensitivity is calculated, but specificity measure has to be modified as the model output did not provide a real "true negative", but only areas with no glomeruli as an opposite of glomerular area). They acknowledge that ninety percent accuracy might be considered a lower limit for a clinically usable device, but also say that further training of the CNN model with additional four stain sets should improve the accuracy going forward. Moreover, the addition of the synchronized display adds significant practical utility to this system. As for the authors, although being a limited proof-of-concept study on a small number of cases, the concept appears sound, and the results were encouraging.

The conclusions of the authors in our opinion reinforce the belief that these machine learning tools are going to become earlier than expected a routine tool for the practicing pathologist, even more after that diagnostic test accuracy studies with the robust methodological design are conducted, as they can answer an increasing need for delivering of expertise in a relatively small field of pathology but with a critical impact on patient management.

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