How Whole Slide Imaging and Machine Learning Can Partner with Renal Pathology

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Digital image analysis is an evolving field, with tremendous potential for clinical applications in renal pathology. Histologic evaluation of stained tissue sections with traditional light microscopy has been the cornerstone of renal pathology since its inception. More recently, technologic advances in whole slide imaging (WSI) are beginning to change the way a pathologist evaluates tissue sections. In a digital pathology workflow, the pathologist may evaluate and diagnose a tissue section on a computer monitor without ever laying hands on a glass slide or light microscope (1). High-throughput slide scanners continue to reduce scan time and improve resolution, accuracy, and image quality (2). WSI has significant advantages over traditional light microscopy, with broad utility in teleconsultation, education, tissue biobanking, image archiving, and digital image analysis. In 2021, the College of American Pathologists updated their guidelines for validation of WSI with the realization that an increasing number of laboratories are using WSI for primary diagnosis (3). In renal pathology, digital pathology and image analysis have predominantly been used in research applications, with limited adoption in clinical workflows (4,5). There are significant barriers to incorporating digital pathology and image analysis into routine practice that will require close collaboration between pathologists, nephrologists, and digital imaging experts.

Basso et al. recently published a machine learning approach to automated classification of glomerular disease among 45 kidney biopsies from patients with minimal change disease (MCD), membranous nephropathy (MN), and thin basement membrane disease (TBMD) (6). Their patient cohort was evenly divided among the three disease categories and included adult men and women. This is a relatively small sample size with a limited number of disease categories but serves as an excellent example of how machine learning can be applied to kidney biopsy evaluation. Basso et al. used automated segmentation of WSI to evaluate a total of 375 glomeruli for 233 features related to tissue color, microstructural textures, and microstructural volumes. These features are not easily evaluated by traditional light microscopy and may provide additional insight into disease pathogenesis. Basso et al. divided their cohort into a training and validation dataset (n=30) to select features for their prediction model. Their prediction model accurately classified 13 of 15 kidney biopsies in the testing dataset (n=15) by placing them into one of three categories (MCD, MN, or TBMD). Their study did not include kidney tissue from healthy control patients or patients with diseases that result in similar histologic findings. So, it is unclear whether this model is broadly generalizable. Although their model did not accurately classify every biopsy, they identified six morphologic and four microstructural features as the best performing biomarkers for classifying kidney biopsies.

The morphologic features that could distinguish between MCD, MN, and TBMD can be placed into three major categories. These categories included ratio of nuclei-to-globular area, globular tuft thickness, and globular circularity. The ratio of nuclei-to-globular area was increased in MCD, which may reflect podocyte injury and hypertrophy. If nuclei-to-globular area is a broad measure of podocyte injury and loss, this metric may have applications beyond distinguishing between MCD, MN, and TBMD. Podocyte depletion is an important prognostic marker for a wide variety of kidney diseases, and podocytopathies constitute a broad spectrum of disorders with highly variable etiologies that require additional workup beyond light microscopy (7). WSI analysis techniques have been developed to quantify podocyte loss, but as this field evolves, digital image analysis of podocytes raises a number of interesting questions (8). Would it be useful to measure podocyte loss in a kidney biopsy, and does that metric contain prognostic information? Are there morphologic features in podocytes suggestive of immune complex deposition, amyloidosis, metabolic storage disorders, or glomerular basement membrane injury? Would this information help to point a renal pathologist toward the right diagnosis? Would these features change over time or correlate with kidney disease progression?

Glomerular tuft thickness was another morphologic feature that was useful for distinguishing between MCD, MN, and TBMD. This feature was increased in MN and decreased in TBMD, which may reflect changes in glomerular basement membrane thickness and mesangial matrix deposition. These findings follow from an earlier study that extracted features such as

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as color, texture, and morphology from glomerular compartments to classify findings in diabetic kidney disease (9). In contrast to TBMD, diabetic kidney disease and MN are characterized by thick glomerular basement membranes. Glomerular basement membrane thickness is typically measured by electron microscopy by averaging serial measurements of a limited number of glomeruli and capillary loops. This process is time-consuming and reserved for patients with a clinical history suspicious for a glomerular basement membrane disorder or glomerular basement membranes that appear abnormal on inspection of light or electron microscopic images. The additional effort needed to measure the glomerular basement membrane is an opportunity to develop WSI analysis tools to do this for us. If this technology was available to renal pathologists, would glomerular basement membrane thickness estimates from WSI be comparable with those obtained from electron microscopy? Would this information help to improve detection of TBMD or provide an indication for genetic testing? How would this information vary in patients with prevalent comorbidities such as diabetes? In the future, WSI analysis studies should strive to demonstrate how their methods can be used to improve patient care.

A notable difference between the study by Basso et al. and earlier studies is the incorporation of microstructural textures into their prediction algorithm. Microstructural textures are not easily appreciated by the human eye, and the four features that helped to categorize between the three disease categories were luminal contrast using wavelets, nuclei energy using wavelets, nuclei variance using color vector LBP, and glomerular correlation using the Gray-Level Co-Occurrence Matrix. In their discussion, Basso et al. report that microstructural features in TBMD and MCD are more heterogeneous among nuclear and luminal structures, whereas MN is more homogeneous. These features are difficult to interpret in the context of kidney disease but could contain valuable information for disease classification. For example, ratio of nuclei-to-glomerular area, luminal contrast using wavelets, and glomerular circularity were the only three features useful for distinguishing between MCD and TBMD. These two disorders cannot be reliably distinguished using light microscopy alone, and there may be an opportunity to develop WSI analysis tools for that purpose. Alternatively, there may be other uses for measuring microstructural textures. For example, could they be used to detect amyloid deposition in glomeruli and vessel walls to prompt a pathologist to order a Congo Red stain? Indeed, it is easy to imagine the analysis methods from Basso et al. being applied to a multitude of kidney diseases such as IgA nephropathy, focal and segmental glomerulosclerosis, and transplant pathology, among others. As we continue to make progress in image analysis, it is likely that for certain diseases, we will be able to identify a number of features such as the ones described that will become a new “gold standard” that could be used in animal models and humans (8,10).

Finding explainable biomarkers may be the most sensible way to get to this “gold standard” or, at least for now, a necessary step to bridge the gap between conventional diagnosis and digital pathology.

In the near future, WSI analysis might supplement a traditional light, immunofluorescence, and electron microscopy workup (Figure 1). The first tools to be developed could tackle the low hanging fruit. Counting the number of normal and sclerotic glomeruli, estimating the proportion of interstitial fibrosis, or quantifying the number of lymphocytes in a tubule are routine tasks that are subject to significant interobserver variability (5,11,12). As the perception of digital pathology and image analysis changes, it is likely that additional tools will be developed to aid in diagnosis and disease categorization. Eventually, integrating these tools with clinical data and other relevant information may lead to robust algorithms that can predict disease behavior in an individualized way.

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See related article, “Explainable Biomarkers for Automated Glomerular and Patient-Level Disease Classification,” on pages 534–545.