Advances in computational nephropathology

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Pathology relies on pathologists' qualitative assessment and semiquantitative measures to characterize the structural and molecular alterations of tissues. Novel analytical methods and recent advances in the computational field, particularly in artificial intelligence and deep learning in pathology, termed computational pathology, have led to widespread applications and advancement in research. Integrating computational approaches into the digital pathology workflow can facilitate the automated, high-throughput analysis of histopathologic images, thereby improving precision, reproducibility, and efficiency in pathology diagnostics. We provide a comprehensive overview of the advancements and applications of computational pathology, specifically in nephropathology. We discuss widely adopted methodological approaches, highlighting their respective strengths and limitations, including quantitative nephropathology (i.e., pathomics), deep learning–based image classification and regression, and nonimage applications (e.g., automated decision support systems for standardizing the reporting of current consensus classifications). Despite the promising potential of these approaches, several challenges remain for successful implementation in routine clinical practice. We highlight technological, regulatory, and ethical challenges, such as computational infrastructure, data privacy, and considerations of environmental sustainability. Looking toward the future, we envisage potential developments that could further transform the field. We are entering a new exciting era, where computational methods are reshaping and redefining kidney pathology, perhaps also renaming our field to "kidnAI" pathology.

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Editor's Note

The application of artificial intelligence–based analysis to kidney pathologic lesions has made exciting progress, made possible by the advent of scanned glass slides to create whole slide images, which then can be analyzed both for quantitation of features a pathologist might see and exciting new approaches, including subvisual features that can enhance understanding of tissue injuries. In this addition to our series on artificial intelligence and machine learning, Hölscher *et al.* from the Boor laboratory provide a review of these specific applications for kidney pathology. The review systematically defines terminology, concepts, and approaches, including machine learning to deep learning, classification, segmentation, and advances in the field of pathomics, detailing progress, potential utilization, and challenges ahead. See the Big Science, Artificial Intelligence, and Machine Learning series at https://www.kidney-international.org/content/bigscience.

Nephropathology provides crucial insights into kidney structure and molecular alterations at the microscopic level, remaining an essential component in the diagnosis, treatment, and research of kidney diseases. In clinical nephropathology, kidney tissue is most often obtained via kidney biopsies. Its assessment requires histopathologic workup, including light microscopy for structural alterations, immunohistochemistry for molecular markers, and, in many cases, electron microscopy for the evaluation of ultrastructural changes. Most of these methods are assessed by pathologists visually and qualitatively, still often performed in an analog manner using microscopes. Semiquantitative histopathologic measures are part of almost every kidney biopsy report. Examples include the Oxford classification of IgA nephropathy (IgAN),[1] or the Banff lesion scores used in the classification of kidney allograft pathology.[2] Albeit providing

clinically relevant and actionable information supplementing the main pathology diagnosis, this traditional approach to pathology has limitations, including low throughput and high interobserver variability.[3,4]

Digitization and automation of pathology are being increasingly adopted in many laboratories worldwide, tackling virtually all steps of the traditional workflow. This process is often termed digital pathology. Digital pathology includes some more basic aspects, like barcoding or laboratory information systems, but also refers to many steps of tissue processing that are increasingly automated using advanced instruments. A major milestone is the development of high-throughput slide scanners, which enable digitization of glass slides to "whole slide images" (WSIs). This transforms the analog workflow using a microscope into a digital workflow, facilitating telepathology (e.g., sharing high-resolution slides or working remotely), leading to higher operational efficiency and greater satisfaction among pathologists.[5] The improved operational efficiency of digital pathology includes faster revision times and quicker external consultation, resulting in a reduction of 19 work hours per week in a large Dutch academic institute for pathology.[6] Digital pathology also enables remote work, offering a potential strategy to counter the diminishing pathology workforce and increasing demands on specialization. Digital workflows also facilitate the implementation of image analysis techniques, particularly those based on artificial intelligence (AI), including machine learning (ML) and deep learning (DL). These technologies introduce new terminology, and the key concepts discussed in this review are summarized in Table 1.

Computational pathology is used as a specific term for computational methods used for the analysis of digital and molecular pathology data, including omics data. It is ideally positioned to help overcome the challenges of manual and semiquantitative analyses in pathology, aligning with the growing emphasis on precision medicine.[7] In image analysis, it mainly uses ML and DL, which have shown promising efficacy in tasks, including image segmentation,[8,9] classification,[10] and regression,[11–13] which will be further discussed in the following sections. DL-based image analyses are already routinely used in pathology practice, currently focusing mainly on cancer pathology. This includes quantitative assessment of (predictive) biomarkers, such as Ki-67 for breast cancer, grading of prostate adenocarcinoma, or cancer detection in lymph nodes. First studies suggested improvements in the diagnostic workflow and precision using some of these tools,[14,15] albeit more studies on this are needed, particularly in nephropathology. Large-scale extraction of quantitative structure-level morphometric data, termed pathomics, has especially gained traction in computational nephropathology, likely because this approach extends the current semiquantitative focus in nephropathology.[8,16–20] Pathomics offers a more standardized, granular, and precise analysis of histopathologic data with a higher throughput compared with traditional histopathology, and it allows for several downstream analyses.

In this review, we examine the current state of computational nephropathology, focusing on DL-based applications for image classification, pathomics, and regression, as well as foundation/large-language models. Our focus lies on DL for computer vision because of its central role and many applications in the digital nephropathology workflow. We emphasize key advancements, comment on existing challenges, and explore potential new frontiers.

Artificial intelligence, machine learning, and deep learning

AI is an umbrella term for all automated systems that perform tasks that are assumed to only be feasible with intelligence,[21] such as visual perception or language processing (Table 1). As there is no exact definition for AI, a variety of computational methods can be assigned to this category. ML is arguably the most prominent subfield of AI. ML refers to AI systems that are not explicitly programmed to perform a task and instead learn this from the data.

The learning process is called *supervised* when (human-made) labels for the respective data points are used for model training. In this case, both the input and the desired output are known (e.g., a WSI as input and a disease diagnosis label as output). Labels can be *weak* or *strong*. A *weakly labeled* dataset consists of image patches from the same WSI, all assigned the label of the entire WSI (e.g., tumor or rejection) regardless of whether individual patches contain the labeled tissue characteristics. An example of a *strongly labeled* dataset would be the exact annotation of the tumor or rejection-relevant areas on each single image patch. In contrast, *unsupervised learning* does not rely on explicitly predefined labels and is based only on properties of the data, such as the similarity between data points. This allows for processing large datasets with only minimal oversight, but limits their applicability to classification, segmentation, and regression tasks. Typical examples of unsupervised learning are clustering, which discovers groups of similar data points, or dimensionality reduction that can be used to visualize the similarity structure of the data in a 2- or 3-dimensional space. An application in digital pathology could be patch clustering, which exploits redundancy in WSIs, potentially discovering morphologic classes (e.g., patches that contain capillaries, fibrosis) without the need to define or annotate them in training data (Song AH. Morphological prototyping for unsupervised slide representation learning in computational pathology. Paper presented at: 2024 IEEE/CVF Conference on Computer Vision and Pattern Recognition (CVPR). June 19–21, 2024; Seattle, Washington, USA). Reinforcement learning is another different learning paradigm where agents are trained through rewards and penalties, enabling them to make decisions within a defined environment. Reinforcement learning is often used in language processing (e.g., a chatbot),

Table 1 | Glossary of terminology

Term	Definition/explanation
WSI	Digital image of an entire histology slide created using a whole slide scanner. Essential step of digital pathology, also enabling efficient computational analysis of histology.
Digital pathology	Encompasses the overall digital workflow of pathology, including acquisition, management, sharing, and analysis of pathology samples, processes, and data. Often, it is used in connection with the specific part of digitization of pathology slides and their handling and analysis.
Computational pathology	Branch of digital pathology that uses computational methods for the analysis of digital and molecular pathology data (including various omics). Currently, major computational methods are based on machine and deep learning.
Telepathology	Performing pathologic diagnosis remotely facilitated by digital pathology.
AI	Umbrella term for computational systems that perform tasks that are assumed to require intelligence.
ML	Subset of AI developing computational systems that learn from data without being explicitly programmed for a given task.
DL	DL, a subset of ML, uses artificial neural networks with multiple layers. Most current computational pathology applications use DL.
Artificial neural network	A computational model consisting of interconnected nodes organized in layers that process information through weighted connections (comparable to an interconnected population of neurons).
CNN	A type of artificial neural network used in DL that is especially designed for image data. The key characteristic of a CNN is the use of image convolution, a mathematical operation that can be used to extract (e.g., texture and edges) from images.
Supervised learning	Learning technique where the model is trained on labeled data, using input-output pairs.
Unsupervised learning	Learning technique where the model is trained on unlabeled data, identifying patterns or structures without predefined labels or outputs.
Cross-validation	Evaluation scheme for classification or segmentation results. The dataset is split into subsets where the training of the classification model is performed on all but one subset, and evaluation is performed on the held-out subset. This process is repeated until each subset has been held out once. The reported classification performance is the average over all these variants.
Foundation model	Large-scale computational model trained on vast amounts of data in a task-agnostic way. Foundation models learn general-purpose representations and patterns, making them a foundation for multiple applications.
Classification	Classification refers to assigning a categorical label to a data point.
Multiple instance learning	Classification scenario where one categorical label is assigned to a collection of images, image patches, or objects (from the same patient). Enables simple annotations, such as labeling an entire WSI as "cancer" (even though not all patches or pixels contain cancerous tissue).
Segmentation	General term for partitioning an image into regions (of interest).
Semantic segmentation	Special case of segmentation assigning a semantic class label (e.g., glomerulus, tubule) to each pixel.
Instance segmentation	Special case of segmentation assigning a combined class and object instance label to each pixel. Unlike semantic segmentation giving the same label "glomerulus" to all pixels covering glomeruli, instance segmentation separates each individual glomerulus (object instance).
IoU	A common metric for evaluating the quality of image segmentation. The IoU is defined as $\frac{\lvert X \cap Y \rvert}{\lvert X \cup Y \rvert}$ where the intersection $\lvert X \cap Y \rvert$ is the overlap between the segmentation X and the human-labeled ground truth Y, whereas the union $\lvert X \cup Y \rvert$ is the entire area covered by the two. The IoU ranges from 0 to 1 (complete overlap).
DSC	A common metric for evaluating the quality of image segmentation and classification in general. The coefficient is defined as $\text{DSC} = \frac{2\lvert X \cap Y \rvert}{\lvert X \rvert + \lvert Y \rvert}$ and measures the overlap between X and Y normalized by the cardinalities $\lvert X \rvert$ and $\lvert Y \rvert$. The DSC ranges from 0 to 1 (complete overlap). It is closely related to the IoU: $\text{DSC} = \frac{2\,\text{IoU}}{1 + \text{IoU}}$.
Regression	Regression refers to the prediction of a dependent target variable (continuous) based on independent predictor variables. A special case is time-to-event regression, where the dependent variable is a time-dependent outcome of interest (e.g., survival).
Pathomics	Comprehensive description of a histopathologic image through a set of quantitative features. The features may serve for statistical data analysis or as the basis for subsequent classification and regression approaches.
End-to-end learning	Learning paradigm where an ML/DL model learns to predict a classification label (or a continuous target variable) directly from the input image (i.e., without an intermediate feature representation [as in pathomics]).
Natural language processing	A technique that enables computers to understand and generate complex human language. Involves the breaking down of segments into smaller units called tokens.

AI, artificial intelligence; CNN, convolutional neural network; DL, deep learning; DSC, Dice-Sørensen coefficient; IoU, intersection over union; ML, machine learning; WSI, whole slide image.

generates a text response, and receives a reward depending on the quality of the response. Thereby, the agent learns a response generation strategy that aims to maximize the sum of future rewards.

DL is a subset of ML that uses artificial neural networks[21] (i.e., algorithms that iteratively process data hierarchically in many layers). The term *deep* refers to the many layers within the neural network. Typically, the deeper a neural network is

(i.e., the more layers it contains), the more complex abstractions it can learn from the data. This allows DL to perform many complex tasks. Typically, training DL requires large datasets, which are increasingly available in medicine. Consequently, DL has driven significant advancements in many image-based medical fields, including computational pathology.

DL in nephropathology

The integration of DL into nephropathology has enhanced various steps in the image analysis process and overall digital pathology workflow (Figure 1). Here, we highlight key applications of DL, including classification, pathomics and regression—3 widely studied approaches in nephropathology. Although these methods provide valuable new insights, they also have inherent limitations and varying degrees of applicability depending on the task (Figure 2). Thus, traditional biostatistical methods remain essential for validating findings, ensuring clinical interpretability and serving as downstream analytical tools for DL-derived data. A comprehensive overview of relevant studies, detailing the DL techniques implemented and datasets used, is provided in Table 2.[8–11,17–20,22–54]

Classification. Classification refers to assigning a categorical label to data. One example is semantic image segmentation, in which classification is performed on a pixel level (discussed below in the section on pathomics). Here, we focus on patient-level classification, where each patient is assigned ≥1 categorical labels (Figure 2). DL-based classifiers learn from complex image features, which are often automatically extracted during training. In many cases, feature extraction is integrated into the neural network as part of end-to-end DL, allowing the model to optimize both feature extraction and classification simultaneously. However, this approach has limitations as the neural networks are typically optimized for 1 specific task and may struggle to generalize to other, unseen tasks.

A multicentric study introduced an end-to-end DL approach for classifying kidney allograft biopsies into 3 classes: normal, rejection, or any other disease.[10] This preliminary diagnosis can help triage biopsies, enhancing diagnostic efficiency. Another study developed a DL approach to

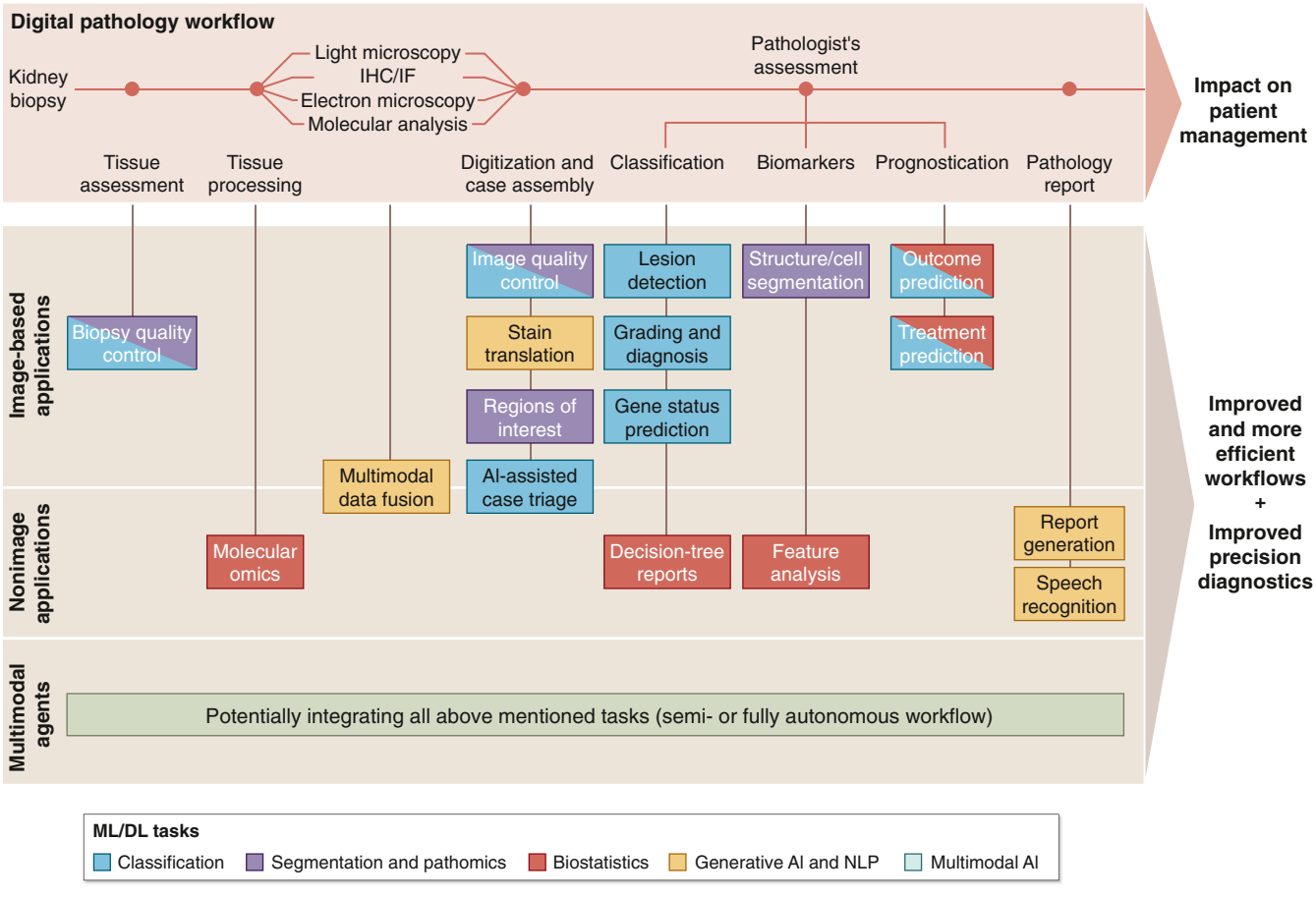
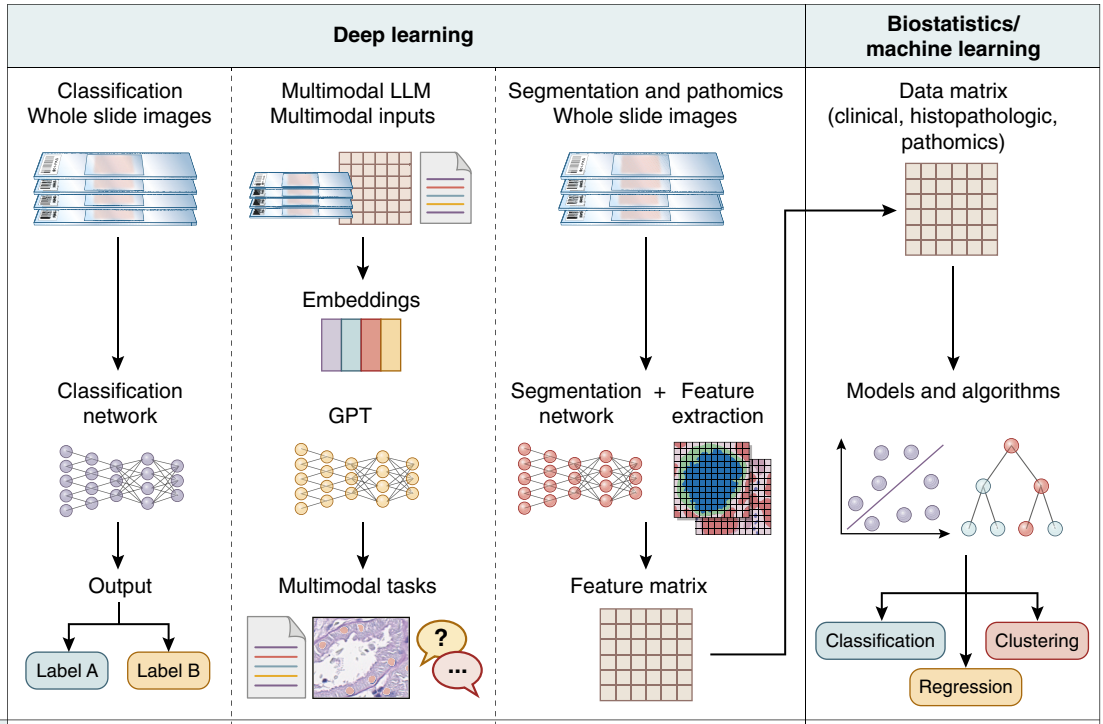


Figure 1 | Overview of the digital pathology workflow and potential possibilities for integration of artificial intelligence (AI) tools. DL, deep learning; IF, immunofluorescence; IHC, immunohistochemistry; ML, machine learning; NLP, natural language processing.



Model development Training data size Supervision	Large Weak	Very large Weak or none	Small to medium Strong	Varies based on model Strong, statistical expertise
Model use Applications Model explainability	Only intended use Low	High flexibility Very low/none	High flexibility High	High flexibility High
Technical aspects Computational requirements Clinical readiness	Can be high Advanced (some approved tools already in clinical use)	Very high Experimental	Low to medium Experimental	Low/very low Established

Figure 2 | Different tasks and frameworks in computational pathology and their respective advantages and limitations. GPT, generative pretrained transformer; LLM, large language model.

rejection subtype classification (T-cell–mediated rejection, antibody-mediated rejection, or other).[44] However, the diagnostic performance in both studies was not as high as in many cancer classification studies. This is likely because of the major challenges for classification of kidney biopsies: diseases can be focal, diseases can have overlapping morphology, and tissue is limited. These might be some of the reasons for the lack of WSI classification studies in computational nephropathology, particularly compared with cancer, in which such studies represent the vast majority. Nevertheless, higher classification performance could be achieved in a scenario where images of individual glomeruli are classified. A recent study on DL-based classification of glomerular lesions, like capillary collapse, or fibrous crescents, achieved promising performance.[41]

However, image classification in digital nephropathology can also expand to other steps of the digital workflow (Figure 1). DL-based classifiers can also be implemented in aspects of quality control. HistoQC, an open-source toolbox for WSI quality control, also incorporates a classifier for detection of pen labels.[49] Another study investigated a smartphone-based tool for adequacy evaluation of kidney biopsy cores directly after needle biopsy, potentially helping clinicians with real-time assessment of kidney tissue quality.[45]

Pathomics. Many studies in nephropathology focus on DL-based segmentation of kidney histology images with subsequent extraction of quantitative features. These features form the basis for a range of downstream applications implementing biostatistical or other DL/ML methods for assigning a diagnosis, characterizing disease states, and predicting disease progression, finding differences between multiple (treatment) groups, or computing morphologic trajectories (Figure 2).

The approach of describing all histopathologic objects in an image through comprehensive morphometric features was termed pathomics, and the enabling technology was termed next-generation morphometry. This follows the terminology of other omics methods, like genomics and next-generation sequencing. Pathomics was acknowledged as 1 of the key advances in nephrology in 2023.[55] The first step in

Table 2 | Overview of current applications of AI tools for computational nephropathology

Study	Datasets	Computational problem	Application
Detection and segmentation			
Kato *et al.* (2015)[22]	Histology, 20 WSIs, rat nephrectomies	Instance segmentation	Glomerulus segmentation (without DL)
Gadermayr *et al.* (2019)[23]	Histology, 24 WSIs, mouse nephrectomies	Instance segmentation	CNN-based glomerulus segmentation
Hermsen *et al.* (2019)[19]	Histology, multicenter, approximately 150 WSIs, biopsies, and nephrectomies, kidney transplant	Instance segmentation	Multistructure segmentation of kidney transplant histology
Marsh *et al.* (2021)[24]	Histology, approximately 150 WSIs, kidney donor biopsies	Tissue property quantification (lesions)	Detection of glomerulosclerosis, comparison with human analysis
Bouteldja *et al.* (2021)[25]	Histology, multicenter, 168 WSIs, animal models	Instance segmentation	Multistructure segmentation of experimental histology, including various animal models
Zheng *et al.* (2021)[26]	Histology, multicenter, approximately 100 WSIs	Tissue property quantification (lesions)	Detection of IFTA, comparison with human analysis
Ginley *et al.* (2021)[27]	Histology, multicenter, approximately 200 WSIs, kidney transplant and DN	Tissue property quantification (lesions)	Detection of glomerulosclerosis and IFTA, comparison with human analysis
Jayapandian *et al.* (2021)[9]	Histology, multicenter, 459 WSIs, 125 biopsies, MCD	Instance segmentation	Multistain and multistructure segmentation of human kidney histology in MCD (NEPTUNE cohort)
Hölscher *et al.* (2023)[8]	Histology, multicenter, 1743 WSIs, 1043 biopsies and nephrectomies	Instance segmentation	Multistructure segmentation of human kidney histology from various diseases, including kidney transplant
Bouteldja *et al.* (2023)[28]	Histology, including IHC, multicenter, 139 WSIs, mouse models, and IgAN	Instance segmentation	Multistructure segmentation of PAS, H&E, silver, and IHC stains
Histomorphometry and pathomics			
Bouteldja *et al.* (2021[25], 2023[28])	Histology, including IHC, multicenter, animal models, and IgAN	Extraction and analysis of handcrafted features	Extraction and analysis of instance-based handcrafted features, including IHC staining
Hermsen *et al.* (2021)[29]	Multiplex IHC, approximately 20 samples, kidney transplant	Extraction and analysis of handcrafted features	Quantification and analysis of peritubular capillaries and immune cells in kidney transplant biopsies
Zimmermann *et al.* (2021)[30]	Immunofluorescence, 110 samples, healthy and ANCA-GN	Extraction and analysis of morphometric features	Morphometric analysis of podocytes in immunofluorescence images from healthy samples and ANCA-GN
Klinkhammer *et al.* (2022)[31]	Histology, single-center, animal models	Extraction and analysis of morphometric features	Analysis of instance-based features for tubules and glomeruli after kidney injury
Lucarelli *et al.* (2023)[32]	Histology, multicenter, 79 WSIs, healthy nephrectomies	Extraction and analysis of morphometric features	Reference analysis of morphometry in healthy nephrectomies
Chen *et al.* (2023)[18]	Histology, multicenter, 280 WSIs, kidney biopsies	Extraction and analysis of morphometric features	Morphometric analysis of peritubular capillaries in the NEPTUNE cohort (including IgAN, FSGS, MCD, and MN)
Hölscher *et al.* (2023)[8]	Histology, multicenter, 1743 WSIs, 1043 biopsies and nephrectomies	Extraction and analysis of pathomics features	Large-scale analysis of extracted pathomics features with association to clinical data and histopathology
Zhu *et al.* (2023)[33]	Histology, pRCT, Alport nephropathy mice	Extraction and analysis of morphometric features	Morphometric analysis to assess the effects of different medications in a mouse model of Alport nephropathy
Unnersjö-Jess *et al.* (2023)[34]	Immunofluorescence, multicenter, approximately 600 images, approximately 135 animal and human samples	Extraction and analysis of morphometric features	Morphometric analysis of podocytes and their foot processes

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Table 2 | (Continued) **Overview of current applications of AI tools for computational nephropathology**

Study	Datasets	Computational problem	Application
Augulis *et al.* (2024)[35]	Histology, multicenter, approximately 1000 WSIs, kidney transplant	Extraction and analysis of morphometric features	Morphometric analysis, including k-means clustering assessing acute and chronic tubulointerstitial injury
Smerkous *et al.* (2024)[36]	Electron microscopy, 93 biopsies, MCD, Fabry nephropathy, DN, living kidney donors	Extraction and analysis of morphometric features	Morphometric analysis of podocyte foot process width in electron microscopy images
Suzuki *et al.* (2025)[37]	Histology, multicenter, approximately 350 samples, DN and nephrosclerosis	Extraction and analysis of morphometric features	Calculation of morphometric injury scores
Classification			
Uchino *et al.* (2020)[38]	Histology, 15,888 patches, 283 kidney biopsies	Classification of image patches	Classification of glomerular lesions
Sato *et al.* (2021)[39]	Histology, 68 patients, IgAN	Image patch clustering	Association of IgAN histology with clinical parameters
Hacking *et al.* (2021)[40]	Electron microscopy, approximately 600 patches	Classification of image patches	Classification of multiple kidney diseases from electron microscopy
Yamaguchi *et al.* (2021)[41]	Histology, multicenter, 10,202 patches, 293 WSIs	Classification of image patches	Classification of multiple kidney diseases from light microscopy
Kers *et al.* (2022)[10]	Histology, multicenter, 5844 WSIs, 1948 kidney transplant biopsies	Image classification (multiple instance learning)	Classification of kidney transplant rejection
Jaugey *et al.* (2023)[42]	Histology, 196 WSIs, 196 patients, IgAN	Image segmentation followed by classification	Classification of MEST-C lesions in IgAN
Yoo *et al.* (2023)[43]	Histopathologic, clinical, and molecular variables, multicenter, approximately 3000 patients, kidney transplant	Decision support system (not AI, but conditional algorithm)	Automated classification system in accordance with the Banff classification for kidney allograft pathology
Ye *et al.* (2024)[44]	Histology, multicenter, 906 WSIs, 302 kidney transplant biopsies	Image classification (multiple instance learning)	Classification of kidney transplant rejection
Eigbire-Molen *et al.* (2024)[45]	Macroscopic biopsy images, 747 biopsy cores, 5 deceased donor kidneys	Image segmentation followed by classification	Smartphone-based classification model for adequacy assessment of kidney biopsy cores
Outcome prediction			
Schena *et al.* (2021)[11]	Clinical variables, 948 patients, IgAN	Classification and time-to-event regression of patient outcomes	Two-step approach of predicting ESKD in patients with IgAN
Yi *et al.* (2022)[46]	Histology, multicenter, approximately 800 WSIs, kidney transplant	Classification of 1-y and long-term outcomes	Prediction of 1-y and long-term kidney transplant graft loss based on a DL-derived score
Zee *et al.* (2022)[17]	Histology, electron microscopy, multicenter, 224 patients, MCD/FSGS	Classification and time-to-event regression of patient outcomes	Classification of disease progression, proteinuria remission, and therapy response in MCD/FSGS (NEPTUNE cohort)
Testa *et al.* (2022)[47]	Histology, approximately 450 patients, IgAN	Classification of patient outcomes based on a developed score	Development of a DL-based predictive score for prediction of ESKD in patients with IgAN
Hölscher *et al.* (2023)[8]	Histology, multicenter, 644 WSIs, 644 patients, IgAN	Time-to-event regression based on pathomics features	Time-to-event regression for 15-y outcomes of IgAN progression based on 5 pathomics features
Cheng *et al.* (2024)[48]	Histology, multicenter, 1138 WSIs from 316 patients, lupus nephritis	Prediction of therapy response	Classification of responders and nonresponders to immunosuppressive treatment in lupus nephritis
Toolboxes			
Janowczyk *et al.* (2019)[49]	Histology	HistoQC: open-source quality control tool for whole slide images	
Pocock *et al.* (2022)[50]	Histology	TIAToolbox: a fully functional and freely available computational pathology pipeline	
Border *et al.* (2022)[51]	Histology	HistoLens: toolkit for quantitative analysis in nephropathology	
Joodaki *et al.* (2023)[20]	Multi-omics	PILOT: method for computing patient distances and disease trajectories based on single-cell/pathomics data	

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Table 2 | (Continued) **Overview of current applications of AI tools for computational nephropathology**

Study	Datasets	Computational problem	Application
Hölscher *et al.* (2024)[52]	Histology, clinical data	tRigon: toolbox for biostatistical downstream analysis of pathomics features and clinical data	
Border *et al.* (2024)[53]	Multi-omics	FUSION: cloud-based application for multimodal analysis of histology, pathomics, and spatial omics	
Mimar *et al.* (2024)[54], Kumar *et al.* (2025)[a]	Histology	ComPRePS: cloud-based suite focused on computational nephropathology, including high-performance computing cluster resources	

AI, artificial intelligence; ANCA-GN, anti-neutrophil cytoplasmic antibody glomerulonephritis; CNN, convolutional neural network; DL, deep learning; DN, diabetic nephropathy; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; H&E, hematoxylin-eosin; IFTA, interstitial fibrosis and tubular atrophy; IgAN, IgA nephropathy; IHC, immunohistochemistry; MCD, minimal change disease; MEST-C, M = mesangial hypercellularity, E = endocapillary proliferation, S = segmental glomerulosclerosis, T = tubular atrophy/interstitial fibrosis, C = crescents; MN, membranous nephropathy; NEPTUNE, Nephrotic Syndrome Study Network; PAS, periodic acid–Schiff; pRCT, preclinical randomized controlled trial; WSI, whole slide image.
[a]Kumar SKC, Paul AS, Abdelazim H, et al. ComPRePS 2.0: enabling massive-scale distributed computing on high-performance computing cluster for histopathological data processing. Paper presented at: SPIE Medical Imaging. February 16–21, 2025; San Diego, California, USA.

a pathomics-based workflow is the detection of histologic structures. This requires DL models that are trained using supervised learning to perform semantic segmentation. Semantic segmentation means that every pixel in each image is assigned a semantic label of the respective structure or cell (e.g., *glomerulus* or *podocyte*) (Table 1). Such segmentation identifies individual histologic objects, from which morphometric data can be extracted. The morphometric data can encompass measurements of shape (e.g., circularity, solidity, and Fourier descriptors), size (e.g., area, diameter), distance (e.g., distance to another object of the same class), texture (e.g., gray-level co-occurrence matrix), color (e.g., intensity of hematoxylin), and many more. The benefit of pathomics is that the extracted feature data are more interpretable and essentially task agnostic, allowing for more flexible downstream applications, compared with the predictions generated by end-to-end DL models (Figure 2).

Quantitative pathomics features enabled comprehensive characterization of a large biopsy cohort with various diseases and validated previous morphometric findings based on clinical data, such as an association of glomerular hypertrophy with high proteinuria in patients with nephrotic syndrome.[8] In IgAN, pathomics enabled a large-scale pseudotime analysis computing a morphometric trajectory depicting progressive deformation of glomeruli during disease transition in IgAN.[8]

Several studies have used pathomics features for data analysis.[31,33,56,57] Many of them have associated the features with clinical parameters, revealing previously unknown associations. Spatial heterogeneity in response to injury was investigated using pathomics analyses in a folic acid mouse model, showing an inverse correlation between capillary density and failed repair.[56] A decrease in the density of peritubular capillaries in fibrotic tissue was confirmed using a pathomics approach, also showing the association of an increase in the aspect ratio of peritubular capillaries with disease progression in podocytopathies or IgAN.[18]

Using a pathomics approach, a kidney donor quality score was developed on the basis of a large cohort of frozen procurement kidney biopsies.[57] This score showed significant correlations with pathologist-derived measurements, but it had superior predictive power for post-transplant kidney function. Retrospective use of the kidney donor quality score in an independent cohort would have led to reduced numbers of discarded kidneys from this cohort (110 of 398).[57] Because of the retrospective nature of the study, the outcome of those additional organs after transplantation remains unclear.

Pathomics is becoming a highly democratized omics approach that can be performed at comparatively low cost when digitized kidney histology is available. Researchers without coding skills can now analyze their samples with freely available software, some of which are hosted online and are usable without the need to buy expensive computational equipment. A possible setup for this could be identifying histologic structures using FUSION (Functional Unit State Identification and Navigation with WSI),[53] extracting morphometric features using HistoLens,[51] and performing downstream analyses with tRigon[52] (Toolbox foR InteGrative [path-]Omics data aNalysis) (Table 1).

Regression. Although classification algorithms assign a categorical label to data, regression algorithms predict a dependent variable (continuous outcome variable) from a set of independent variables (e.g., pathomics features). These dependent variables can be anthropometric measurements (e.g., blood pressure), laboratory values (e.g., proteinuria), continuous histopathologic scores (e.g., interstitial fibrosis), or time-to-event outcomes (e.g., time to development of end-stage-kidney disease). When the dependent outcome variable is already known, regression can serve to analyze which of the features are predictive for the outcome, and to characterize the relationship between features and outcome. These relationships can be linear or polynomial, depending on the modeling function.

Although some studies on end-to-end image regression exist in pathology, in nephropathology, regression algorithms are predominantly applied in the context of pathomics feature analyses. In human nephrectomy samples, glomerular histomorphometry was associated with patient age, sex (based on biological characteristics such as chromosomes, hormones, and sex organs), and laboratory estimates of kidney function.[32] Large-scale analysis revealed a decrease in cortical glomerular density and an increase in glomerular size, signaling hypertrophy associated with chronic kidney disease.

Time-to-event regression analyzes the time until a clinically relevant outcome occurs, such as end-stage-kidney disease, graft failure after kidney transplantation, or overall patient mortality. Multiple studies have demonstrated prediction of the time until end-stage-kidney disease in patients with IgAN, using regression models based on pathomics features,[8] DL-derived scores,[47] and clinical as well as histopathologic variables.[11] For prediction of graft loss after kidney transplantation, a multicentric study implemented a composite damage score based on DL-derived features of pathologic lesions of tubules and interstitial and mononuclear leukocyte infiltration.[46] The scores from kidney biopsies 12 months after transplantation were predictive of long-term graft loss, exceeding the performance of Banff scores or clinical predictors.

In the future, regression will be further improved by deep phenotyping of kidney tissue, resulting in more precise and robust predictors, as well as by more advanced statistical techniques, such as Bayesian linear regression, which can incorporate prior information.

Nonimage applications. Although DL is widely known for its broad applicability in image analysis, its capabilities extend beyond visual data to a variety of nonimage tasks within the digital nephropathology workflow. A prominent technique in this domain is natural language processing, a subform of ML, which enables the extraction of insights from texts, such as written pathology reports or electronic health records.[58] Natural language processing can break down complex human language into smaller manageable units, or tokens, allowing for disease classification from textual descriptions or mining patient data for specific conditions (Figure 1). Beyond text mining, ML algorithms can also use clinical and histopathologic descriptors, bypassing the need for images to automate the generation of diagnoses and pathology reports in line with established guidelines, such as the Banff classification system.[43] These descriptors can also be applied to common prediction tasks, such as disease progression and treatment response.[17] With the advent of large-language models, the scope of nonimage applications in nephropathology might likely further expand.

Explainability, robustness, and causality. One challenge of DL models is their *black box* nature (i.e., the inability of humans to understand the exact *reasoning* of the DL in its internal decision-making process). Trust in model output can be improved through rigorous external validation using large, diverse, and ideally multicentric datasets that differ from those used for training. Although such validation improves confidence and generalizability, it does not necessarily enhance interpretability. Explainability is particularly important in classification tasks, where *post hoc* methods like saliency maps (i.e., heat maps highlighting image regions most influential for a decision) can offer visual insights. In segmentation tasks, interpretability is more intuitive, as image predictions can be directly compared with annotated ground truths (by overlaying the predicted maps with the original histology picture). More detailed explanations of visualization techniques for explainable AI and their implementation can be found elsewhere.[59] Despite these methods, researchers should be careful in inferring pathophysiological principles as model predictions are based on statistical associations and not causal relationships. With the emerging field of causal inference,[60] more studies will investigate these cause-and-effect relationships, potentially leading to novel biological insights.

Challenges in the adoption

Despite great advances in computational nephropathology research, the adoption of digital pathology solutions in clinical pathology laboratories, including any DL-based diagnostic support or tests, is progressing rather slowly in many countries. This has several reasons (Figure 3), especially because the technological and associated financial hurdles remain high. Pathology digitization is associated with considerable costs for the initial investment in scanners, hardware, and software, and their long-term maintenance. The large size of WSIs requires considerable (secure) hardware storage and fast network connections, and the computational requirements of DL can be substantial. Although some studies indicated potential long-term financial benefits from implementing digital pathology workflows,[6,15] these systems are currently perceived as economically inefficient compared with traditional analog approaches. This is aggravated by the lack of reimbursement mechanisms for costs associated with DL-based technologies across many, if not most, health care systems. As with other developing technologies, the hope is that the price will decrease in the future, making digital pathology more broadly applicable. Professional pathology organizations will need to engage in political advocacy efforts to secure appropriate reimbursement. Until then, the advantages offered by digital pathology and DL applications (i.e., enhanced capabilities for remote work,[61] improved quality assurance, better resource sharing, streamlined operational processes, and increased diagnostic efficacy) will be the main propellers of digital pathology adoption.

Another technological challenge is in the integration and interoperability of digital pathology systems not only with existing (hospital) information systems and other external software but also with various components of digital pathology itself. Currently, there is a lack of a standard application programming interface between the pathology laboratory information systems and digital pathology viewers/image management systems/picture archiving and communication system, and DL algorithms. Also, we are lacking a standard file format for WSIs, and numerous vendor-specific solutions are being used. One solution could be an open-source standardized interface, such as the one developed by the EcosysteM for Pathology diagnostics with AI Assistance consortium, which was already implemented by some vendors in their products.[62] Like radiology, which is using Digital Imaging and Communications in Medicine (DICOM) standards internationally, a similar approach will

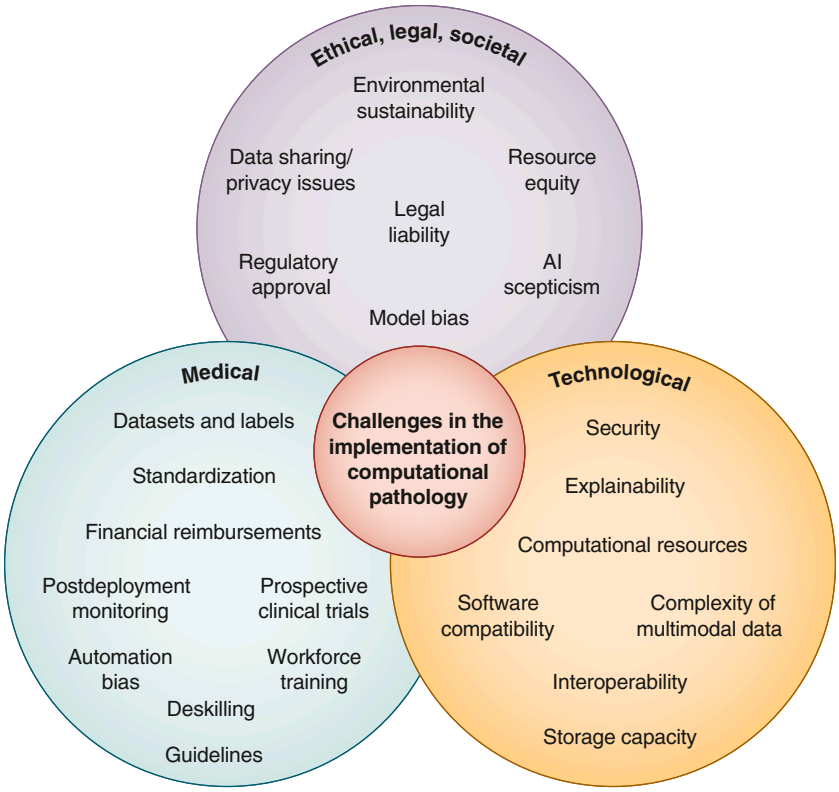

Figure 3 | Challenges in the implementation of artificial intelligence (AI)–based tools within a computational pathology framework. These challenges can be divided into medical, technological, as well as ethical, legal, and societal challenges.

likely be needed in digital pathology to achieve improved interoperability and standardization. Currently, DICOM—although available—is not routinely used in pathology. Tools to convert vendor-specific formats into DICOM are already available (including the WSIDicomizer[63]). Using the DICOM format in pathology could have advantages. DICOM incorporates slide metadata, which can include diagnosis or patient age, facilitating research use. A vendor-neutral format would be preferable for institutes, especially when changing vendors. However, in contrast to radiology, many images are connected to a patient, and storing the right metadata in the right image file is challenging. In addition, incorporation of metadata into a slide would require in-depth integration with the laboratory information system, which is often challenging by itself. Given this complexity, there is currently neither clear guidance nor regulations. Regulatory and compliance issues represent another hurdle in the implementation of digital pathology. The varying, and often absent, regulatory landscapes remain problematic, considering that there is a need for health authority approvals for primary diagnostic procedures in digital pathology. This is also because of a lack of standardized test methods, including those for WSI scanners and image quality assessment. Regarding regulatory approvals, there is currently (beginning 2025) only a single US Food and Drug Administration–approved DL for pathology diagnostics (for prostate cancer). Many relevant factors are falling under regulatory scrutiny, such as the definition of specific scenarios for use cases and intended applications, their implications, conducting thorough validation protocols, and providing comprehensive guidelines for implementation and utilization. Available checklists can facilitate the development of AI/DL models in a regulatory-applicable way and with meaningful implementation in the diagnostic patient path.[64]

The environmental sustainability and energy consumption of DL models, not only in pathology, are crucial, yet often overlooked aspects.[65,66] This occurs especially given the growing model complexity with billions of trainable parameters and the ongoing energy crisis. Such considerations are important for successful implementation into routine, which processes large amounts of samples and resulting (large WSI) data on an everyday basis.

Currently, we are also lacking rigorous medical validation of using DL in pathology and nephropathology. Until the beginning of 2025, there was no randomized prospective study analyzing the utility of DL diagnostics in pathology. Using dedicated study designs, in other fields such as radiology or emergency medicine, ethical concerns were raised about possible negative impacts on patient outcomes stemming from currently available DL assistance.[67] Specifically, designed validation trials, and enhanced accuracy, alongside careful, improved quality assurance,[5] better resource sharing, streamlined operational processes,[6] and increased diagnostic efficacy,[68] will be the main propellers of digital pathology adoption.

Nephropathology faces several unique challenges. For successful DL development, large and granular datasets are required.[69] This is particularly because of the kidneys' intricate microanatomic architecture, a large heterogeneity of often rare renal pathologies,[70] and the variability in the implemented staining techniques. With few exceptions, the currently available datasets lack deep phenotypic data and, in most cases, are not well controlled for specific research questions. Often, datasets are available in various formats and acquired using different tests, making their integration difficult. Integration of data across emerging (inter-)national initiatives, like CureGN,[71] the Kidney Precision Medicine Project,[72] or NURTuRE,[73] will be needed to provide sufficient inclusiveness regarding heterogeneity of patient populations. In the future, access to randomized clinical trial data and setting up international cooperations will likely be essential to move the field forward. Other specific challenges in nephropathology are the specialized techniques used. Rarely does any other pathology area use specific histologic stains, immunofluorescence, or electron microscopy. Developing digital pathology and DL solutions tailored for such specific techniques will be required but might be challenging under *in vitro* diagnostic regulatory requirements given the small market.

Addressing these technological, regulatory, and infrastructural challenges will require a comprehensive approach involving medical and technological advancements, regulatory clarity, institutional support, and ongoing education and training for pathology professionals (Figure 3). Key components will be interdisciplinary cooperation to standardize data formats and establish robust validation frameworks as well as the continuous advocacy for regulatory clarity and economic incentives to ensure sustainable integration into health care systems and provide economic plannability for developers. Initial data on increased patient safety, responding costs,[74] and early trials in cancer biomarker pathology already exist,[15] exemplifying how the pathology community should extend generating robust scientific evidence supporting the implementation of digital pathology and AI. The generation of large and high-quality datasets, coupled with international collaborations, will be instrumental in advancing nephropathology-specific applications. Smaller or partial implementation strategies might be another interim strategy for adoption of digital pathology and AI with reduced costs.

Future perspectives

Computational pathology is a fast-evolving field. Here, we discuss some potential key advancements and emerging technologies that might be expected to further advance the field in the future.

Novel imaging modalities. Advances in nondestructive tissue imaging now allow visualization across multiple scales, from whole-organ or tissue samples up to subcellular resolution. For example, hierarchical phase-contrast tomography leverages high-energy X-rays to image intact human tissue, providing deep penetration and nanoscale resolution, ideal for mapping complex kidney architectures, such as entire nephrons.[75]

Many of these emerging imaging techniques enable 3-dimensional, comprehensive visualization of tissues in high resolution. Often, DL is used for segmentation of these 3-dimensional datasets. Although most current pathomics approaches in nephropathology deal with 2-dimensional images, the integration of 3-dimensional data on multiple scales could offer new insights in studying complex histologic architecture and injury patterns. Nondestructive imaging, if performed sufficiently fast or in fixed tissues, also preserves tissue for subsequent molecular analysis. Although interesting for research applications, whether such methods will find integration in clinical pathology diagnostics remains unclear.

Novel molecular methods. Novel molecular approaches, particularly spatial omics methods, are already substantially advancing kidney research. These spatial omics methods represent a significant advancement in molecular biology, enabling the high-throughput analysis of several molecules (RNA: transcriptomics; proteins: proteomics; and metabolites: metabolomics) while maintaining spatial context.[76] This spatial context is crucial for understanding complex cellular interactions and tissue organization, providing insights that traditional molecular methods might miss. The integration of multiple omics datasets through spatial analysis has particularly enhanced our understanding of tissue architecture and cellular relationships.[77] Another promising technique is hyperplex immunofluorescence imaging, enabling simultaneous detection of up to 40 protein and RNA biomarkers within the same tissue section in a high-throughput manner, often preserving the tissue for additional analyses.[78] Analysis of the large-scale data derived from such molecular omics methods is another important component of computational pathology. In our review, we focus more on image-based computational pathology approaches, and more detailed discussion of molecular methods can be found elsewhere.[79,80] Importantly, pathomics approaches can provide the missing link in spatial tissue organization and morphology, complementing and extending the molecular diagnostics. This spatial context is crucial for understanding complex cellular interactions and tissue organization as reflected in the pathology of kidney fibrosis,[81] providing insights that traditional molecular methods might miss. Such combined (path-)omics analyses have already shown potential in oncological pathology (e.g., by tracking molecular alterations in pancreatic lesions in 3 dimensions).[82] Combining and integrating multiple omics datasets remains challenging, and novel computational approaches can be demanding and in part still need to be developed. Although invaluable for research, the value for clinical diagnostics remains to be determined.

Foundation and large-language models. Foundation models are large-scale ML models that are trained on vast amounts of data. These models capture comprehensive data

representations and can be fine-tuned for many downstream tasks with minimal task-specific data. Although foundation models use similar DL architectures as traditional approaches, they differ in several key aspects, especially model size, training paradigms, and computing requirements. Foundation models are significantly deeper than task-specific DL. The number of trainable parameters in foundation models typically is in the range of billions or trillions, whereas in traditional DL models, millions of trainable parameters are used. Consequently, training a foundation model requires enormous computational resources—often dedicated hardware clusters. In contrast, traditional DL models can often be trained on a high-performance workstation. These computing requirements are reflected in energy consumption not only for training but also inference, with potential implications for their respective costs and environmental sustainability.

Among the different types of foundation models, large language models trained on text data have garnered significant attention in the public since the introduction of ChatGPT, an app based on generative pretrained transformers.[83] Vision foundation models are trained specifically for image data. Integration of such vision models into multimodal foundation models (e.g., large language vision models) has recently been introduced for medical datasets, enabling agents like PathChat.[84] PathChat allows a user to specify a computer vision task using free text only. Such multimodal foundation models introduce possibilities for the development of intelligent agents assisting in medical practice by integrating the multimodal data generated each day for each patient to suggest diagnostic and therapeutic procedures[85,86] (Figure 2).

Especially for oncologic pathology, foundation models are increasingly establishing themselves as promising general-purpose tools for tasks such as cancer detection, subtyping, mutation status analysis, survival prediction, and report generation. CTransPath, the first foundation model for computational pathology, is a 28-million parameter vision transformer model trained on 32,000 WSIs.[87] Since its publication in 2022, models have rapidly expanded in terms of their training data size, model size, and task diversity. Current state-of-the-art computational pathology foundation models, such as Virchow2G, consist of 1.8 billion parameters and are trained on 3.1 million WSIs.[88] UNI, which was trained on >77 terabytes of data, covers 20 different tissue types and can perform 34 representative computational tasks, including classifying up to 108 cancer types in the OncoTree system.[89] However, kidney tissue often only accounts for a small proportion of the datasets used and mostly consists of kidney cancer slides. For instance, kidney tissue comprises <4% in the CTransPath and <3% in the Virchow2G training data. Because of the lack of large-scale public datasets, no specific foundation models for nephropathology have been developed so far.

So-called multiagent frameworks encompass multiple specialized autonomous agents that collaborate toward a user-specified goal. The idea is that collaborative agents can achieve tasks that go beyond the capabilities of single agents.[90] In principle, the tools are already available to build a multiagent system that analyzes clinical data associated with a kidney biopsy, analyzes the histology, orders potential additional tests, and writes a comprehensive analysis report (Figure 1). Importantly, this is different from a single multimodal model in that, in multiagent systems, each agent can have a distinct method that is best suited for the specific data or problem aspect it analyzes. Such frameworks might develop toward generalist medical AI[85] and become medical companions for physicians, not just in pathology.

Conclusion

Computational nephropathology is transforming our ability to analyze kidney histopathology and is expected to significantly contribute to both nephrology research and clinical diagnostics. By integrating artificial intelligence techniques into the digital and molecular workflow, we can enhance diagnostic precision, reveal novel morphomolecular relationships, and enable the exploration of previously unapproachable research questions. The further growing number of studies in this field demonstrates its promising potential, but several technological, ethical, and regulatory challenges remain before its widespread clinical implementation. As AI, DL, and novel analytical models in imaging and molecular omics continue to evolve, including the advent of foundation models and multimodal AI, they offer exciting opportunities toward the goal of better understanding and managing diseases and sustaining human health.

DISCLOSURE

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