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14. ABSTRACT
Nearly one third of all adults with Systemic Lupus Erythematosus (SLE) present with lupus nephritis (LN) at diagnosis and up to two thirds manifest kidney involvement during the course of the disease with higher prevalence in minority populations particularly those of African ancestry. Furthermore, as many as 10% of patients with LN will progress to end-stage and require dialysis and/or kidney transplant. The ability to accurately identify LN patients at risk for progression could shift much of the current management paradigm from treatment to prevention. However, the prognostic significance of histopathologic classification of LN, the most current arising from a collaboration between the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) in 2004 is controversial. Therefore, novel approaches are required to obtain continuous, quantitative data to improve accuracy, reproducibility, and prognostic utility. Digital pathology, a dynamic, image-based environment for the acquisition, management, and analysis of information generated from digitized images, is emerging in the setting of clinical trials and research, including kidney disease, but has yet to be applied to lupus nephritis biopsy interpretation in a large cohort. We hypothesize that digital pathology and image analysis approaches will improve the prognostic utility of the kidney biopsy in lupus nephritis and allow more efficacious treatment approaches**.** In this project we will apply detailed quantitative morphologic scoring, computer-aided, semi-automated, morphometric analysis with deep learning segmentation, and integrative molecular approaches to establish improved methods of kidney biopsy interpretation in lupus nephritis.

15. SUBJECT TERMS
None listed.

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1. Introduction

One third of all adults with SLE present with lupus nephritis (LN) at diagnosis and up to two thirds manifest kidney involvement during the course of the disease. Furthermore, as many as 10% of patients with LN will progress to end-stage and require dialysis and/or kidney transplant. Importantly, 10-year survival improves dramatically if disease remission can be achieved, necessitating improvements in our understanding and classification of LN. The ability to accurately identify LN patients at risk for progression could shift the current management paradigm from treatment to prevention. Thus, novel approaches are required to obtain continuous, quantitative data to improve accuracy, reproducibility, and prognostic utility. The goal of our proposal is to improve the utility of the kidney biopsy to predict disease progression in lupus nephritis by applying quantitative morphology and computer-aided, semi-automated, morphometric analysis. In addition, a subset of lupus nephritis patients has whole genome gene expression data from glomerular and tubulointerstitial compartment. Thus, we will also be able to correlate clinically predictive pathology features with transcriptomic profiles to highlight candidate molecular pathways for biomarker discovery and novel treatment approaches. By combining kidney morphometrics and gene expression profiling, we will explore our governing hypothesis that inherent in the structural complexity of the kidney biopsy is quantifiable information that is predictive of clinical outcomes and underlying disease biology.

2. Keywords

Lupus nephritis, kidney biopsy, digital pathology, transcriptomics, deep learning, glomerulonephritis.

3. Accomplishments

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- **What was accomplished under these goals?**

Aim 1: Identify quantitative morphologic predictors of clinical outcomes and clinically meaningful clusters of patients with common morphologic profiles using the NDPSS

NEPTUNE Digital Pathology Scoring System (NDPSS) was developed to capture the morphologic complexity of glomerular disease. It capitalizes on the relatively recent availability of digital pathology technology to provide a detailed, quantitative, and highly granular assessment of the kidney biopsy by evaluating the presence and extent of discrete structural changes ("descriptors") in glomeruli, tubulointerstitium, and vessels. Data collection is objective and agnostic to conventional categories.[1,2] Thus, the **objective** of this aim is to apply the NDPSS (modified for lupus nephritis) to the scanned WSIs we have collected of LN patients from Clinical Phenotyping Resource and Biobank Core (CPROBE), of the University of Michigan George M. O'Brien Kidney Center, and correlate with clinical outcomes. We will test the **hypothesis** that LN patients can be categorized into clinically meaningful clusters based on morphologic descriptors of structural changes of the glomeruli, tubulointerstitium, and vessels.

As previously described,[3,4] morphologic descriptors have been designed for pathology related to FSGS and MCD from the NEPTUNE cohort. The pathologists for this project have added to the original list of 63 glomerular, tubulointerstitial, and vascular descriptors to accommodate pathology features seen in lupus nephritis, largely adding features relevant to inflammation – glomerulonephritis, tubulointerstitial nephritis, arteritis, etc. We now have 77 glomerular, 22 tubulointerstitial, and 7 vascular morphologic descriptors that cover all known pathologic features of LN. **Table 1** shows a partial list of the descriptors we will use, grouped by class.

Table 1. Selected quantitative morphologic "descriptors" for lupus nephritis

Global (G) glomerular obliteration	Segmental (S) glomerular obliteration	Podocyte and parietal cell injury
G sclerosis without hyalinosis	S sclerosis	Visceral epithelial hypertrophy
G sclerosis with hyalinosis	S tip lesion	Visceral epithelial hyperplasia
G deflation	S collapse	Parietal epithelial hypertrophy
G collapse	S perihilar sclerosis	Parietal epithelial hyperplasia
G mesangial sclerosis	Adhesion without sclerosis	Hyalin droplets in epithelial cells
Mesangial expansion	**Endocapillary hypercellularity (EndoCH)**	**Extracapillary hypercellularity (ExtraCH), Crescent**
S or G mesangial hypercellularity	S or G EndoCH	S or G cellular ExtraCH
S or G mesangial matrix expansion	S or G EndoCH with neutrophils	S or G fibrocellular ExtraCH
S or G mesangiolysis	S or G endocapillary neutrophils	S or G extracapillary fibrosis
S or G mesangial neutrophils	without EndoCH ("circulating" neutrophils)	Neutrophils in crescent
Tubulointerstitial (% of cortex)		**Arterioles (%)**
Tubular atrophy	Tubulointerstitial inflammation:	Arterio- and arteriolosclerosis
Interstitial fibrosis	lymphocytes, plasma cells,	Arterio- and arteriolohyalinosis
Tubular dilatation	neutrohilis in tubules or	Arteritis
Tubular cell necrosis/apoptosis	interstitium.	Fibrin deposition
Interstitial edema	Peritubular capillaritis	Myxomatous change

(G) global; (S) segmental

For WSIs of each kidney biopsy, every glomerulus from available stained sections (H&E, PAS, trichrome, and Jones silver - standard histochemical stains for kidney biopsies) is given a number (glomerulus 1, 2, 3 …N) by a trained technician annotator. Each glomerulus is numbered accordingly through all available sections and a digital image of each glomerulus is extracted from the WSI at the same time. Thus, each glomerulus from the WSIs of the kidney biopsies will have digital images available for scoring from every section in which the glomerulus is seen (generally 4-6 glomerular section images per glomerulus). Digital glomerular images are randomized and sent to pathologists along with a scoresheet. Each glomerular image is scored by two pathologists. Discrepancies are adjudicated between the two pathologists or a third when necessary. Scoresheets are collected by Dr. Hodgin's staff and randomization removed. Descriptor scores from each digital section image (section-level data) are combined for descriptor scores at the whole glomerulus level (glomerulus-level data). The frequency of each descriptor is then calculated at the level of the patient (patient-level data) as a percentage of glomeruli with that descriptor for further analysis. Tubulointerstitial and vascular descriptor scoring is performed by the pathologist viewing all available WSIs across all histochemical stains for each biopsy. Scoring is focused on the cortex.

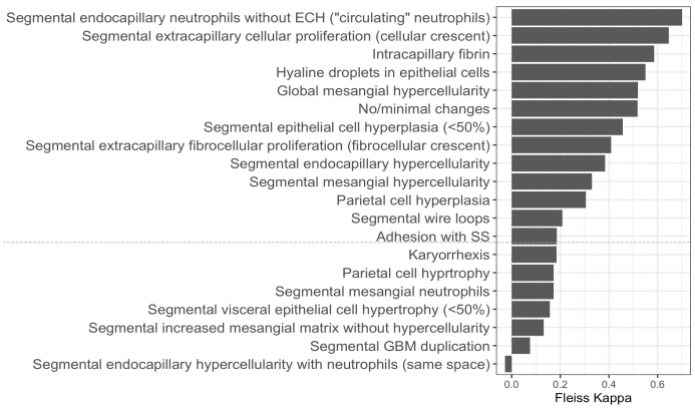

Figure 1. Initial reproducibility testing of glomerular descriptors for lupus nephritis from 50 glomerular images. Only the 20 descriptors with maximum prevalence >5% are shown.

Reproducibility of the NDPSS has been previously tested[3] and optimized,[4] and the majority of descriptors were shown to have moderate (kappa 0.4 to 0.6) to good (kappa 0.6 to 0.8) reproducibility. For this project proposal, Drs. Hodgin and Nast have been training for descriptor scoring. During training sessions, descriptors from example glomerular, tubulointerstitial, and arteriolar images are reviewed and discussed. Fifty glomerular images (H&E, PAS, trichrome, and Jones silver stained) from lupus nephritis kidney biopsies were descriptor-scored. **Figure 1** displays the Fleiss kappa statistic from morphologic descriptors with maximum prevalence >5% over pathologists. We defined maximum prevalence as the largest proportion of glomeruli assigned a particular descriptor by any pathologist. The Fleiss

kappa statistic is a measure of agreement that ranges from -1 to 1 with 1 indicating perfect agreement and -1 indicating perfect disagreement. As shown in the figure, 40% of the descriptors had moderate to good agreement (kappa >0.4), which is in line with NDPSS reproducibility. When descriptors are grouped by segmental and global characteristics (e.g. 'segmental mesangial hypercellularity' and 'global mesangial hypercellularity' combined to 'any mesangial hypercellularity'), agreement scores significantly improved (data not shown), indicating that in many cases disagreement is not whether the presence of the descriptor is seen by all three pathologists, but there is disagreement on the amount of the descriptor. We will perform another round of training to assess reproducibility improvement and will then complete the scoring of LN biopsies in CPROBE. When a substantial number of cases have been scored (approximately half of those available) we will begin correlations with outcome as described.

Aim 2: Identify morphometric predictors of clinical outcomes using computer-aided image analysis algorithms
Quantitate histologic primitives using image segmentation with deep learning algorithms

To bring deep learning segmentation to our research team at the University of Michigan, we have been developing DL image analysis algorithms to segment histologic primitives of the kidney biopsy. In order to capture histological features that reflect chronic, irreversible damage, we have focused on the trichrome stained slides with the latest semantic segmentation deep learning architecture called DeepLab V3+ developed by Google to automatically segment kidney structures with various augmentation methods to improve the accuracy. A total of 136 images were selected randomly from whole-slide images with a size of approximately 3000×3000 pixels (720 μm × 720 μm). We used predefined classes: open glomeruli, arterioles, globally sclerosed glomeruli (not shown), interstitium, and tubules. The performance of our deep learning model for the multiclass segmentation was assessed on the test set (20% of all data). **Figure 2** shows an example result of automatic segmentation by our deep learning model. The global accuracy was 0.95 and the highest accuracy for the individual class was 0.98 for tubules (**Table 2**). In addition, we have used DeepLab V3+ with ResNet18 to automatically segment glomerular mesangium from extracted images of PAS stained glomerular tuft (**Figure 3**). A total of 92 images with matching images of ground-truth annotated mesangium were used (70% for training, 15% for validation, and 15% for testing). Global accuracy was 0.95 and accuracy for mesangial segmentation was 0.83.

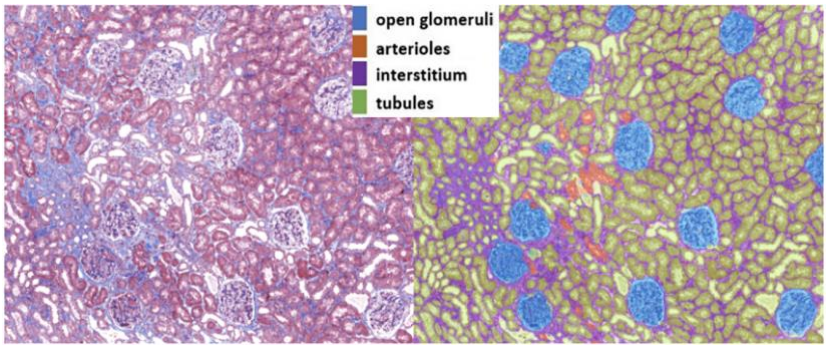

Figure 2. Automatic segmentation by deep learning. The left is the original trichrome stained image and the right is the result of the segmentation by our trained model (DeepLab V3+ with ResNet18).

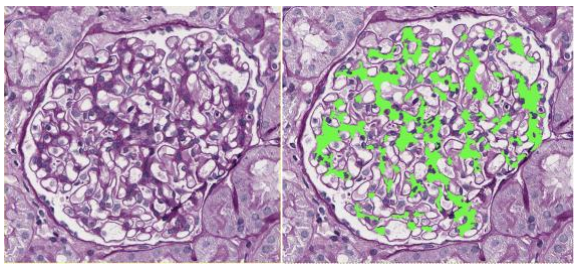

Figure 3. DL-segmentation of mesangium (green) using DeepLab V3+ with ResNet18 in PAS-stained glomeruli.

Table 2. Accuracies of deep learning segmentation for 5 classes using trichrome and 1 class for PAS stained glomeruli						
Structure	**Open glomeruli**	**Arterioles**	**GS glomeruli**	**Interstitium**	**Tubules**	**Mesangium**
Accuracy	0.95	0.87	0.88	0.91	0.98	0.83

Generating accurate DL segmentation algorithms requires carefully annotated ground truth. For this project, we will use digital images of H&E, PAS, and trichrome stained kidney, though we expect PAS will be the most useful as it displays very good nuclear morphology and clearly shows basement membranes that separate kidney structures. To generate ground truth for our selected histologic primitives, we have been using manual annotation, supervised by Dr. Hodgin, or the image processing package FIJI/ImageJ (Rasband, Image J, NIH; imageJ.net/FIJI) to generate ground truth binary masks when possible.[5,6] **Figure 4** is an example of ground truth binary masks we generated for glomerular

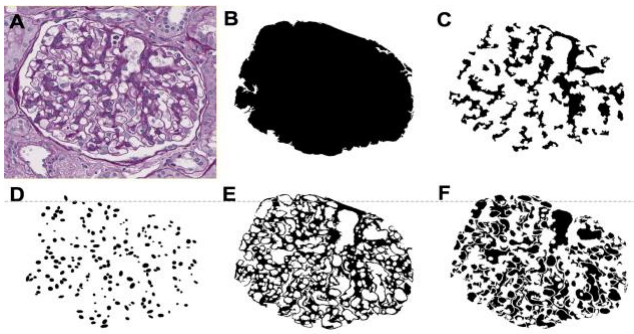

Figure 4. Ground truth images as black/white binary masks generated by FIJI/ImageJ. Original image (A), glomerular tuft (B), mesangium (C), glomerular nuclei (D), all glomerular matrix, and glomerular capillary space (F).

tuft (B), mesangium (C), and nuclei (D) from a PAS stained glomerulus. In addition, shown are ground truth binary masks for all glomerular matrix (E) and open capillary space (F). In a notable recent publication computational segmentation of glomerular nuclei, matrix, and capillary space were used to quantify the structural progression of diabetic glomerulopathy from human kidney biopsies.[7] All extracted images are being normalized using the Reinhard stain normalization method,[8] which is an important step for annotation, clustering and classification tasks. We compute the global mean and standard deviation of each channel in the LAB color space for the Reinhard normalization method for all data and use them as reference values to normalize our image data.

Based on features of the ISN/RPS classification, NIH activity and chronicity indices, and expert knowledge of the Pathology Team, we have selected a group of histologic primitives for DL segmentation and morphometry that are likely to correlate with outcome data. **Table 3** shows a list of basic structures and features (histologic primitives) for segmentation, our basic methods of measurements, and examples of morphometric data we can derive. Morphometric data from each segmented feature will vary depending on its characteristics. For example, globally sclerotic glomeruli will be shown as a percentage of all glomeruli. The area of the interstitium will be shown as fractional interstitial area of the total cortex. The morphometric data is derived at the patient level to facilitate correlation with clinical data.

Table 3. Selected histopathology features and structures (histologic primitives) for deep learning segmentation and morphometry

Segment	Measure	Calculate
Structures:	Area of structure (e.g. glomeruli, tubules, interstitium, arterioles)	- Percentage of within all of cortex or per structure (e.g. glomeruli, tubules, interstitium, arterioles)
Glomerular unit and tuft	Area of glomerular matrix	
Globally sclerotic glomeruli	Area of interstitial matrix	- Estimated glomerular volume (Weibel-Gomez formula)
Glomerular mesangium	Number of all nuclei	
Tubules	Number of immune cell nuclei	- Fractional area (e.g. fractional interstitial area of cortex; fractional mesangial area of glomerular tuft)
Interstitium		
Arterioles		- All nuclei or immune cell nuclei density over cortex or specific structure: glomerular, tubular, interstitial, arteriolar total and immune cell cellularity
Cells:		
Nuclei, all		
Immune cell nuclei: mononuclear, neutrophil, plasma cell		
Matrix: fibrosis, sclerosis		

Morphometric analysis using BoW approach

Unsupervised machine learning methods have been successfully used to associate kidney pathology with renal survival using digital images of trichrome stained kidney biopsies.[9] The **objective** of this aim is to apply an unsupervised machine learning method to cluster image patterns or features from WSIs of the LN biopsies. We will test the **hypothesis** that LN patients from CPROBE can be categorized into clinically meaningful clusters based on unsupervised machine learning detection of histopathological image patterns or features using a Bag-of-Words (BoWs) approach used by the Rao laboratory.[10]

We have constructed a predictive model to classify patient's level of kidney function using BoWs. WSIs of trichrome stained kidney biopsy sections were obtained from 57 patients in our digital pathology image repository from the CPROBE. In this first iteration of BoW we used kidney biopsies from patients with FSGS, MCD, LN, and diabetic nephropathy. The BoW workflow (**Figure 5**) was applied to the cortex of each WSI. Patches of trichrome stained kidney cortex, measuring 256x256 pixels, were used for feature extraction. Extracted features were clustered through K-means clustering with the optimal number of clusters determined to be 9. A histogram representation for each biopsy sample was created using the frequency of each cluster

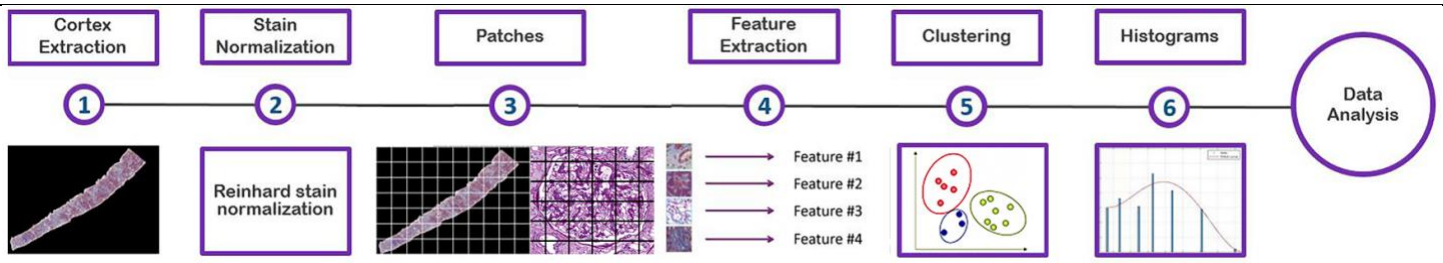

Figure 5. Workflow for the unsupervised learning using a bag-of-words paradigm.

type. We performed K-means clustering and obtained cluster indices, centroid location, and distance from each point to every centroid for the analysis.

Figure 6 shows (a) nine centroids (or phenotypes) and (b) a representative example of cortex and (c) its cluster map with colored patches. Patients were dichotomized according to estimated glomerular filtration rate

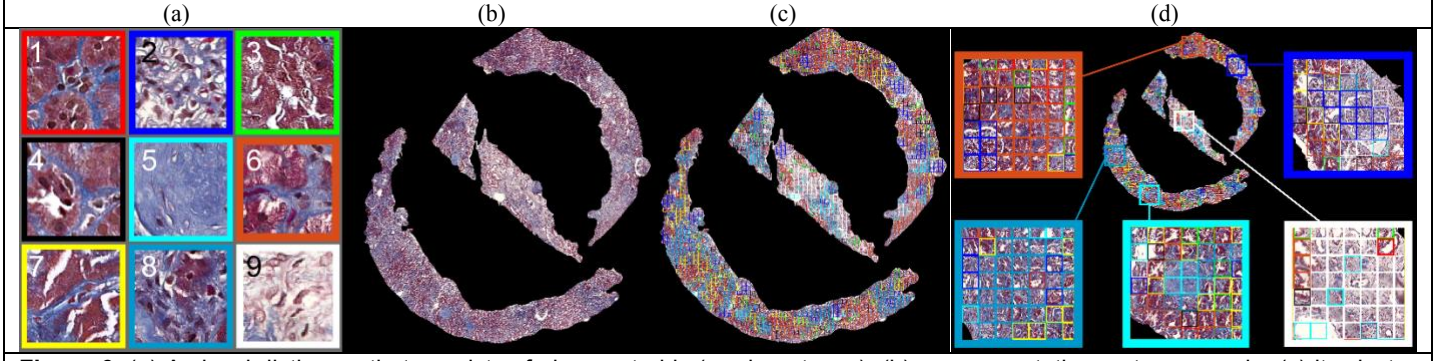

Figure 6. (a) A visual dictionary that consists of nine centroids (or phenotypes), (b) a representative cortex example, (c) its cluster map with colored patches, each 256 × 256 pixel box represented by one of the 9 in (a), and (d) examples of zoomed images.

(eGFR) greater than or less than 60. We used a random forest model as a classifier to predict association with dichotomized eGFR. We identified important features (top 7 centroids) in terms of the level of the kidney function. The out-of-bag (OOB) error from the random forest was 0.07, the sensitivity was 0.94 and specificity was 0.89. Using the frequency of the top 7 centroids to predict eGFR, we found the area under ROC curve (AUC) is 0.93 and 95% confidence interval is 0.86 – 1.0. The accuracy was 0.93 for this model. Next we will apply this approach to only LN cases.

Aim 3: Identify transcriptomic determinants that associate with disease morphologic and morphometric profiles

In this Aim, we will investigate the hypothesis that transcriptional profiling of clinically predictive morphologic and morphometric descriptors and patient clusters will reveal unique molecular mechanisms of lupus nephritis and add molecular plausibility to our quantitative assessments from Aims 1 and 2. An association analysis between the histologic primitives and BoW features, and the tissue gene expression data will be performed using C-PROBE samples (~30 cases) with linked histology and gene ex-pression datasets (both glomerular and tubulointerstitial compartments). As described above and expected, the progress on this Aim will not be possible until the second year of funding and thus no data update is provided.

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- **What opportunities for training and professional development has the project provided?** Nothing to Report.

- **How were the results disseminated to communities of interest?** Nothing to Report.

- **What do you plan to do during the next reporting period to accomplish the goals?**

In the second and last year of funding, we will complete the descriptor scoring in Aim 1, obtain morphometric data from the glomerular and tubulointerstitial compartments, and expand and rerun the BoW algorithm to focus on biopsies from patients with LN. These findings will be correlated with clinical outcome and will be correlated with gene expression from glomerular and tubulointerstitial compartments (Aim 3).

4. Impact

- **What was the impact on the development of the principal discipline(s) of the project?** Nothing to Report.
- **What was the impact on other disciplines?** Nothing to Report.
- **What was the impact on technology transfer?** Nothing to Report.
- **What was the impact on society beyond science and technology?** Nothing to Report.

5. Changes/Problems

- **Changes in approach and reasons for change.** Nothing to Report.
- **Actual or anticipated problems or delays and actions or plans to resolve them.** Nothing to Report.
- **Changes that had a significant impact on expenditures.** Nothing to Report.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.** Nothing to Report.
- **Significant changes in use or care of human subjects.** Nothing to Report.
- **Significant changes in use or care of vertebrate animals.** Nothing to Report.
- **Significant changes in use of biohazards and/or select agents.** Nothing to Report.

6. Products

- **Journal publications.** Nothing to Report.

- **Books or other non-periodical, one-time publications.** Nothing to Report.

- **Other publications, conference papers, and presentations.**

"Computational Pathology and Lupus Nephritis". Oral presentation by Dr. Hodgin to the Accelerated Medicines Partnership for Lupus Nephritis consortium on March 10th, 2021.

- **Website(s) or other Internet site(s).** Nothing to Report.

- **Technologies or techniques.** Nothing to Report.

- **Inventions, patent applications, and/or licenses.** Nothing to Report.

7. Participants & Other Collaborating Organizations

- **What individuals have worked on the project?**

Name: Jeffrey B Hodgin, MD PhD

Project Role: PD/PI

Nearest person month worked: 1

Contribution to Project: Dr. Hodgin has been in charge of all project organization and planning and supervision of Drs. Yang and Lee. He has also performed pathology scoring with Dr. Nast

Name: Arvind Rao, PhD

Project Role: co-PD/PI

Nearest person month worked: 1

Contribution to Project: Dr. Rao has been in charge of project organization and planning concerning digital pathology and image analysis approaches and in supervision of Dr. Lee's work.

Name: Joonsang Lee, PhD

Project Role: Research Lab Specialist Senior

Nearest person month worked: 4

Contribution to Project: Dr. Lee has been implementing deep learning and morphometric approaches to analyze the kidney biopsy images.

Name: Cynthia Nast

Project Role:

Nearest person month worked: 1

Contribution to Project: Dr. Nast has performed pathology scoring with Dr. Hodgin.

Name: Yingbao Yang, PhD

Project Role: Research Lab Technician Intermediate

Nearest person month worked: 4

Contribution to Project: Dr. Yang has organized and prepared all digital images for analysis.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?** Nothing to Report.
- **What other organizations were involved as partners?** With the exception of working with Dr. Nast, renal pathologist at Cedars-Sinai, there is Nothing to Report.

8. Special Reporting Requirements. Nothing to Report.

9. Appendices. Nothing to Report.