As will become increasingly evident as the reader advances through this supplement, glomerular diseases are a leading cause of renal morbidity and failure in dogs. In animals with glomerular lesions that have not progressed to an end stage, renal biopsy has potential to provide a definitive diagnosis and important clinical information about the type, severity, and biologic behavior of the underlying injury. However, current diagnostic practices and classification schemes based on limited light microscopic information have permitted only a loose grouping of pathologic categories that have had little discriminating potential to direct therapeutic intervention or provide outcome assessment. This limiting (light microscopic) characterization of glomerular disease has provided only a myopic interpretation of the glomerular lesions. With little possibility to characterize subtle distinctions, kidney biopsy became relatively abandoned as a diagnostic tool in veterinary medicine during most of the 20th century. In human patients, differences in discrete glomerular diseases based on more robust pathologic imaging permits expanded clinical and pathologic characterization of glomerular disease prompting specific treatment recommendations and outcome predictions. It seemed reasonable that similar pathologic disparity and potential for more discriminating pathologic characterization was likely for canine glomerular disease if evaluated more precisely.

In 2005 with sponsorship of Novartis Animal Health, an international gathering of veterinary nephrologists and nephropathologists convened the International Veterinary Renal Pathology Initiative (IVRPI) at Utrecht, the Netherlands, to develop a vision to more accurately characterize canine glomerular pathology. The goals of the initiative included:

1. Establishment of an international consortium with expertise in nephrology and nephropathology for collaborative and interactive review of kidney biopsies and integration of these disparate disciplines.
2. Establishment of an international infrastructure for routine diagnostic pathology based on high-resolution light, immunofluorescent, and electron microscopic imaging considered essential to assess glomerular pathology.
3. Establishment of a global network to capture standardized pathologic and clinical information from dogs with naturally occurring glomerular disease and to provide world-wide access to all diagnostic imagery seamlessly with the corresponding clinical data.
4. Establishment of a validated, consensus-based classification scheme for canine glomerular disease to facilitate therapeutic decision making, outcomes assessment, and prospective clinical research.

In 2007, as a follow-up to the Utrecht initiative, the WSAVA Renal Standardization Project (WSAVA RSP) was launched under the auspices of the World Small Animal Veterinary Association with generous support from Hill’s Pet Nutrition and Bayer Animal Health. The overarching purpose of this ambitious 6-year project was to apply a broad array of diagnostic and communication technologies to promote a paradigm shift in the diagnostic and clinical approach to glomerular diseases in veterinary medicine. Fundamentally, the goals of the WSAVA RSP were to fulfill the vision of the Utrecht initiative to more accurately characterize glomerular diseases in dogs employing light, transmission electron, and immunofluorescent microscopy as diagnostic modalities, and to relate the specific pathologic findings to the clinicopathologic presentations and outcomes in proteinuric dogs. Within this overview, a variety of specific achievements were envisioned, which have established a scaffold for the future pathologic assessment of glomerular disease in dogs in addition to other visionary directions.

The WSAVA Renal Standardization Project is now approaching the completion of this initial phase of the project and has made exceptional progress advancing the proposed infrastructure, defining the discipline of nephropathology, characterizing the expression of canine glomerular disease, and establishing a prototype classification system for canine glomerular disease. The
international expertise dedicated to the study of glomerular pathology and glomerular disease expanded from the study group initially assembled in 2005 to include 12 nephropathologists and 9 nephrologists from 5 countries. The Nephropathology Team has descriptively characterized more than 100 light microscopic and 30 electron micrographic features or patterns of the canine glomerulus and surrounding renal structures. Each feature has been archived in a digital glossary to provide an illustrative reference to the established future standards.

The current classification and nomenclature for canine glomerular disease has been based on human classification schemes and on the foundation of light microscopic criteria. To provide greater objectivity, diagnostic consistency, and flexibility to the pathologic categorization, a scoring system has been established to characterize the extent and magnitude of identifiable lesions of renal glomeruli, the tubular epithelium, interstitium, and vasculature. Using this scoring system, the Nephropathology Team has documented as proof-of-concept in a subset of 90 canine patients a new paradigm for the subjective assessment and objective classification of canine glomerular disease. The paradigm establishes distinct pathologic groupings ("diagnoses") based on traditional pathologic principals in addition to consensus scoring of the lesion array produced with the multiple imaging modalities. This fusion of subjective assessment and quantitative annotation has been modeled further with sophisticated statistical algorithms (cluster analysis) to objectively arrange and group patients with statistically distinct morphologic associations, which likely represent unique disease entities. The features of these morphologic clusters will constitute the foundations to assign statistically derived morphologic diagnoses (eg, "membranous nephropathy") that are specific and appropriate for dogs. The resulting prototype classification system will enable more precise and consistent classification of glomerular diseases than previously possible and will be subjected to subsequent validation.

The study also has confirmed that the spectrum of recognizable or variant glomerulopathies is more extensive than appreciated previously by conventional light microscopy. Even traditional light microscopic diagnoses including amyloidosis, membranoproliferative glomerulonephritis, and membranous nephropathy can be shown to encompass a variety of morphologic differences when examined more comprehensively by light microscopy and ultrastructurally with transmission electron microscopy. What remains to be defined is whether these identifiable differences represent true pathophysiologic variations or stages of expression of a singular disease or distinctly different pathologic entities constituting different diseases.

Equally focused, the Nephrology Team is tasked to correlate the pathologic diagnoses with clinical and clinicopathologic data to identify patterns of findings that constitute distinct canine glomerular disease features that might be expected to have foreseeable outcomes or predictable responses to treatment. These correlations will be used to render a finalized morphologic and clinicopathologic classification scheme for canine glomerular disease that can be applied uniformly among veterinary nephropathologists and nephrologists once validated. The Clinical Team similarly has established a scoring scheme founded on over 130 numerical and categorical clinical attributes on the same dogs with glomerular disease whose kidney biopsies are under review. Each attribute is independently evaluated and scored by clinical team members from supplied medical records, consultation with the submitting clinician, or from data entered into the established medical database. Subsequently, an international review session is held for each patient, and a consensus score is established for each attribute by the team. The clinical attributes list is scheduled for the same statistical logistics to test if there are defined groupings of clinical features in patients with distinctly associated morphologic characteristics or pathologic diagnoses. By this analytical approach, the Project anticipates the possibility that canine glomerular disease can be more precisely defined and classified on the basis of both the morphologic features (light, electron, and immunofluorescent microscopy) and the patterns of the clinical and pathologic response to the glomerular insult.

The WSAVA RSP is unique throughout the world and represents a global diagnostic resource for general and specialty veterinarians and the pet owning public. The comprehensive light, immunofluorescent, and electron microscopic services have extended the diagnostic capabilities for renal diseases to a level of sophistication and precision standard in human nephrology. It has also been visionary to embrace burgeoning technological advances in digital pathology, distance conferencing, and global data sharing that portended revolutionary directions for the global assessment and management of disease and innovative opportunity for research and teaching interactions that no longer are constrained by institutional alliance, world location, or budgetary limitations. These visions for the 21st century were exploited ahead of their time and stand today as models for international clinical and academic collaborations. Today, nephrology and nephropathology are advancing to subspecialty niches within their respective disciplines of internal medicine and anatomic pathology. The nephrologist and nephropathologist have had little difficulty recognizing overt injury to the glomerulus, but the nephropathologist has had limited therapeutic strategies with defined clinical and pathophysiologic correlations; and the nephrophopathologist has been constrained by an overly subjective and imprecise morphologic classification system based primarily on hematoxylin and eosin staining and light microscopy. Today, veterinary nephrologists have begun to appreciate the existence of a broad spectrum of distinct glomerular entities, which heretofore have been loosely grouped into a limited collection of pathologic categories. Nephropathology also is poised (and mandated) to abandon its simplistic, subjective, and
outdated classification scheme for glomerular disease that has been generally adopted from human pathology.

Veterinary medicine also is emerging from an era of regional diseases, local diagnostic facilities, and geographically limited consultative expertise to an expanded international community seeking the same quality of service, patient care, and access to expert opinion. The technologies validated by the WSAVA RSP have made it possible for a veterinarian in a rural community anywhere in the world, with no regional expertise to aid or guide clinical decisions, to avail state-of-the-art diagnostics and international experts in kidney disease to counsel on his/her patients in near real time. The WSAVA RSP embraced recent advances in digital pathology, telemedicine, distance conferencing, and international patient registries and data sharing to expand the conventional knowledgebase and facilitate rapid and worldwide access to authoritative consensus and expert opinion to any and all who seek it.

The foundations of the Project are two regional Diagnostic Renal Pathology Centers that have been established as a global network with identical, quality-controlled procedures to process and share high-resolution digital micrographic images of kidney specimens for light, immunofluorescent, and transmission electron microscopic evaluation. On the foundations of a prototype center developed under the auspices of the WSAVA RSP by Dr George Lees at Texas A&M University in the USA, a second center was established at Utrecht University in the Netherlands under the direction of Drs Astrid van Dongen and Joco van der Lugt. At the core of each center is an Aperio digital slide scanning system for the production of virtual whole-slide images that can be reviewed simultaneously throughout the world and a robust digital imaging and data management platform to facilitate sharing and analysis of the digital imagery. (Figs 1, 2)

An extensive electronic relational medical and pathologic database was developed to archive and integrate the pathologic and clinical information, to facilitate data analysis, and to provide a platform for international data sharing. The database enables compilation of all historical, clinical, laboratory, therapeutic, follow-up, and outcome data for the entire course of a patient’s disease and management. The clinical database also stands poised to serve as an international registry for banking clinical information from animals with kidney disease. The clinical database has been merged with the pathologic database to establish a single seamless interface to all clinical and pathologic information, which is available in real time throughout the world. A critical component for the initiative was a forum for international case discussion to integrate clinical nephrology with nephropathology. Advances in web-based conferencing provided an extremely effective and high-quality solution for simultaneous and interactive review of clinical features and digital imagery by the combined nephrology and nephropathology consortium assembled throughout the world. From

Fig 1. Conceptual illustration of whole-slide digital pathology in which specimens from a kidney biopsy mounted on glass slides (left) are digitally processed to produce a “virtual slide” (center). The “virtual slide” can be accessed instantaneously from any world location and evaluated with equivalent or better quality and diagnostic potential as a conventional light microscope when viewed with the “virtual microscope” on the computer.
these case conferences, consensus-based, clinical or pathologic diagnoses are rendered to formulate the prototypical glomerular classification scheme or to provide expert analysis and diagnosis of a distant patient. The case review platform can serve secondarily as an effective venue for advanced specialty training in nephrology and nephropathology and to facilitate impromptu scientific exchange and insightful opinion by noted authorities.

The WSAVA RSP has placed into practice a quantum shift vision for the clinical and pathologic assessment of glomerular disease in dogs. The strategic and implemented components of this vision hold great promise to improve the recognition and management of glomerular disease and to promote the exchange of knowledge to all segments of the veterinary profession. The technological components of the project stand as proof-of-concept that veterinary medicine stands ready to enter a new era of diagnostic and clinical opportunities, which can extend to all corners of the world. It further signals the future delivery of veterinary services by distant technologies and announces the arrival of telehealth and distant web-based training and consultative possibilities.

### Footnotes

a Original IVRPI Committee: Claudio Brovida (Italy), Cathy Brown (USA), Larry Cowgill (USA), Jonathan Elliott (UK), Roel Goldschmeding (Netherlands), Reidun Heiene (Norway), Johan Jansen (Norway), George Lees (USA), David Polzin (Chair, USA), Kinji Shirota (Japan), Bill Spangler (USA), Shelly Vaden (USA), Astrid van Dongen (Netherlands)
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References