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Edited by Xin Jin (Joseph) Zhou , Zoltan G. Laszik , Tibor Nadasdy , Vivette D. D'Agati  
Frontmatter  
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# Silva's Diagnostic Renal Pathology

Second Edition

# Silva's Diagnostic Renal Pathology

## Second Edition

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ZHOU

To my loving wife, Jian Wang, and our wonderful children,  
Jason and Jaclyn

LASZIK

To my beautiful wife, Erika, and our wonderful children,  
Nandi, Laura, and Aron

NADASDY

To my wife, Gyongyi, and my daughters, Krisztina and Orsolya

D'AGATI

To my devoted husband, Edward Imperatore, and my loving  
children, Edward and Paul, without whose constant support  
and encouragement my academic career would not be possible

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## Foreword

This is written to acknowledge all those who make our subspecialty wonderful and fun. Indeed, all of what we know in renal pathology is because of the efforts of an extraordinary number of investigators both clinical and experimental throughout the world. We know them and the essential work they produce through the medical literature, courses, lectures, and “hall-way discussions.” This book is a compilation of so much work, effort, talent, knowledge, and creativity by so many.

The Renal Pathology Club (now known as the Renal Pathology Society) started with a dozen or two pathologists, but has grown considerably to encompass 500 renal pathologists from over 35 countries. We meet regularly to learn from each other and to consider what is known and what is unknown (and what needs to be studied). In fact, not only do all the members of the Renal Pathology Society contribute to all our knowledge, but help “raise the bar” for all of us through presentations at the various Congresses, courses like the Columbia P&S Renal Biopsy course (under the able direction of Dr. Vivette D'Agati), and much less visiting professorships at many university medical schools. I am proud to be a part of the collegium of renal pathologists throughout the world. My own best times are with my colleagues in nephrology and I thank you for that. Indeed, it was not unusual to sit at a dinner table (e.g., Renal Pathology Society, etc.) with renal pathologists I knew so many years from the literature but not yet met in person. Recalling their papers led to the beginning of a personal friendship. We are colleagues, collaborators, confidants, competitors (collegial competition serves to make us all better) and (sometimes) characters whose legends will continue for quite some time (no names here). The peer-review process continues to improve our papers; we all have reviewed and been reviewed. I have yet to receive the old saw that says: “Your paper is both original and interesting. Unfortunately what is interesting is already known, and what is original is wrong” (or close to that)! We also owe a great acknowledgment to our stimulating fellows in nephropathology. I have been fortunate enough to have a number of great ones, several of whom are co-authors and co-editors of this book.

We pathologists serve as physician's physicians, better known as consultants. It is my experience that the most important (and fun) part of our profession is the interaction with the nephrologists. Our nephrology colleagues (in my case Drs. G. Appel, R. Toto, K. Kaufman, and a large number of others)

continue to teach us as much as we teach them, for the benefit of all. We renal pathologists can still provide the best indicators of diagnosis, prognosis, guide the therapy, heurism – what to do next for the patient – and method(s) of proper follow-up for the patient's renal disease. As Dr. Pirani (one of my many mentors) once wrote: “Pathology and the microscope are where function meets morphology”.

A few years ago, I did a small survey of approximately three dozen renowned pathologists with great consultation services (covering most of the organ systems). I learned a lot in this survey about the major traits of great consultants, including: (a) knowing what the clinician needed to know and being an indispensable part of the health care delivery team for the patient; (b) open and clear communication – knowing what you know and what you don't know, and not being afraid of asking others for their judgment on difficult cases; (c) obtaining the entire relevant clinical and laboratory data and integrating all sources of information; (d) remaining up-to-date on the literature; (e) incorporating new advances and appropriately validated technology; (f) knowing the outcome of your diagnosis; and (g) as the old saying goes – availability, affability, accountability, and ability. There are many more aspects of being and becoming the best consultant possible, and it is probably the most pleasurable and important endeavor we perform.

However, our work is not done. The renal biopsy continues to be the “gold standard” clinical studies in the foreseeable future. If one looks at the great Nephrology texts, one will see that many (usually a majority) of the chapters are divided by diseases only the renal pathologist can diagnose with certainty in the individual patient. However, as Dr. Pirani has stated, “the renal biopsy will hopefully lead to studies and techniques, that will replace the renal biopsy.” Advances in immunology, molecular biology, and the “-omics” will make the future a very exciting place to be. In part, the future is already here, and we are seeing creative renal investigators introducing new techniques for more exact diagnosis, prognosis, therapeutic regimens, and methods of follow-up, much less the essential understanding of the basic mechanisms. There are lots of things that still need to be done (even more than before, now that we are learning what we didn't know).

Finally, as Dr. Pirani once said: “we owe to the patients a gratitude and responsibility.” If not for these patients and



Foreword

a huge effort by so many, we would not have advanced as far as we have. On behalf of all those we serve – our patients, physicians, students, and those to come – I/we thank you for all you have done, are doing, and will do in the future. Progress will

continue. As Enrico Fermi once said at the end of a speech: “Now, let’s get to work.”

*Fred Silva, MD*

## Preface to the First Edition

If you do not know the names of things, the knowledge of them is lost, too.

– Carl Linnaeus

Throughout our many combined years of teaching renal pathology, we have been impressed by the challenges to students learning the subject for the first time. There are many reasons why the study of renal pathology is considered difficult. First, there is insufficient knowledge of the normal histology/structure of the kidney. Second, one disease can manifest many different morphologic patterns, while a particular morphologic pattern can be produced by different diseases or etiologic factors. And finally, several different names (synonyms) have been applied to particular patterns or diseases. Yet, the many years of teaching have convinced us that there can be a systematic and orderly approach to the study of renal pathology. Therefore, a new book emphasizing an algorithmic, deductive approach to the interpretation of renal pathology seemed timely. This book organizes the various renal patterns and diseases in a standardized fashion, with emphasis on clinical–pathologic correlations. We have limited our inclusion of renal morphologic patterns to comparatively stable taxonomic groups covering the major diagnostic entities accepted by the published literature.

Standardized names and terminology are essential for communication among renal experts, whether they are clinicians or pathologists. The terminology used in this book is generally consistent with that used by most North American renal pathologists. Wherever possible, we have applied the widely recognized International Nomenclature of Disease (IND), a joint project of the Council for International Organization of Medical Sciences and the World Health Organization. The purpose is to ease communications and facilitate the storage and retrieval of medical information. As noted by the IND, a “few diseases have a single recognized name; most have several different . . . names. The principle objective of the IND is to provide . . . a single recommended name” (specific, unambiguous, self-descriptive, simple, and based on cause whenever feasible). It is meant to be a truly international language of disease. The importance of precise terminology and diagnostic criteria cannot be overstated.

The approach and classification used in this book are neither unique nor original. They are based on the “capture” of ideas from the many members of the Renal Pathology Society, Inc.,

and from major courses in the field, such as Medical Diseases of the Kidney, a postgraduate course held annually for more than 30 years by the Columbia University College of Physicians and Surgeons in New York City, under the direction of Dr. Vivette D'Agati. The approach to renal biopsy has been influenced enormously by Dr. Conrad L. Pirani, and it should come as no surprise that the editors of this book have either studied directly under him (V.D., F.G.S.) or been mentored directly by Dr. Pirani's student, Dr. Silva (X.J.Z., Z.L., and T.N.).

A useful classification (and the subsequent approach to diagnosis) should be based on the following requirements.

1. The classification should be clinically relevant and provide useful information to the clinician (about diagnosis, prognosis, identification of clinical subsets, optimal choice of therapy, evaluation of response to therapy, and future management).
2. It should be based on facts (reflecting the ideals of evidence-based medicine), be scientifically correct, and incorporate our current level of biologic understanding.
3. It should be relatively easy to use by pathologists throughout the world and be reproducible between observers.

The approach of *Silva's Diagnostic Renal Pathology*, which incorporates these principles, is morphologically based and designed for practicing anatomic (and renal) pathologists. By maintaining a high level of expertise in renal pathology, pathologists can ensure that the current trend of increasing use of renal biopsy for diagnosis and patient management will continue.

Many algorithms that collectively detail the clinical, laboratory, and pathologic patterns of renal disease have been included. These algorithms, based upon clinical and morphologic findings, will allow one to find the correct diagnosis. The algorithms provide a simplified road map that directs the reader to the major patterns of interest. To this end, we have adopted a combined “clinical and pathologic” classification scheme in this book. We have always found it ironic that most dictionaries, atlases, and textbooks require a priori that one knows what something is (e.g., what the diagnosis is and how to spell a particular word) in order to look it up and find the relevant entry. We hope that this book will eliminate that problem.

We believe that the approach in this book, neither final nor perfect, will allow the student to discover and categorize the

Preface to the First Edition

type of renal involvement, correlate it with the clinical and laboratory findings, and determine the renal prognosis and optimal therapy. Of course, there are always “varieties” or “cross-overs” or “dual diseases,” which render exact classification difficult. Nonetheless, a good description is always reliable. More atypical or unusual cases are likely to be referred for renal biopsy, because the clinically obvious cases (e.g., minimal change nephrotic syndrome in children, acute postinfectious glomerulonephritis, diabetic nephropathy with retinopathy) often are not biopsied unless they exhibit atypical features. In the end, it is the renal morphology interpreted in an informed clinical context that leads pathologists to an accurate diagnosis. Although this book is intended as a practical guide for the diagnostic pathologist with primary responsibility for renal biopsy interpretation, as “clinical biologists” we should not lose sight of the pathogenetic factors behind the morphology. Thus, we have included a short section on “Pathogenesis” in each of the chapters.

The authors each bring their own unique personal insights to their individual chapters. However, we have attempted to bind them together through a unanimity of purpose, as reflected in their similar styles and analytic approaches.

At each step, the renal pathologist is integrating knowledge about the light microscopy, fluorescence microscopy, electron microscopy, renal functional studies, urinalysis, systemic findings, medication history, serologies, and radiologic studies. It is

this multidisciplinary approach that constitutes the most rewarding aspect of renal pathology. Despite the complexity of the subject material, we hope that the approach outlined in this book will provide a user-friendly guide into this fascinating field.

As our mentor, Dr. Conrad Pirani, often said, it is important that clinical nephrologists and pathologists work closely together for the good of the patient. The pathologist cannot function in isolation. The most difficult diagnostic dilemmas can usually be solved by combining the knowledge of clinician and pathologist on an individual case. As Dr. Pirani has stated in a renal biopsy textbook, “[s]tructure and function have finally met at the microscope.” The pathologist and nephrologist can learn a great deal from each other by reviewing cases together over the multiheaded microscope.

Lastly, we would like to thank the renal patients, physicians, and pathologists without whom we would not have had the opportunity to collect these biopsy materials for teaching purposes. We thank them for providing us with such valuable illustrative cases. We, pathologists, strive to understand what we see and place it in a diagnostic context that guides the nephrologist toward more specific therapies. As better and more targeted therapies are developed, an accurate biopsy interpretation will become even more important. It is highly likely that the renal biopsy will continue to be cost-effective for all those we serve – our patients and our clinicians.

## Preface to the Second Edition

When we launched the first edition of the *Silva's Diagnostic Renal Pathology*, we envisioned to fill a niche somewhere between the existing encyclopedic texts and the various atlases. The format of this new book should emphasize on “how to approach the diagnosis of renal diseases” using an algorithmic and deductive method. We have adopted a combined “clinical and pathologic” classification scheme in this book so that the readers can quickly focus on the aspect of the condition of interest. Since the publication of this book seven years ago, several quite positive book reviews were published in prestigious nephrology and pathology journals. The responses from pathologists, nephrologists, and trainees both in pathology and nephrology are overwhelmingly laudatory. The requests from readers and the advances in all aspects of kidney diseases mandate a new edition.

Although with considerable excitement, we started the second edition with great humility and trepidation. Dr. Fred Silva, a remarkable medical scholar and nephropathologist, has decided to hand over the baton to us. All editors have been mentored by him at certain stages of our careers, and we shall always be in his debt for his mentoring, friendship, and

support. Even though Dr. Silva was not directly involved in editing this edition, his guidance and wisdom is invaluable to the success of the second edition.

Major advances have occurred in renal pathology in recent years requiring significant changes in the content of this book. All chapters have been extensively revised and updated. Content on renal development has been added in Chapter 1. Rapidly progressive glomerulonephritis has become a separate chapter owing to the clinical importance of and enormous new advances in crescentic glomerulonephritis. Given the interesting parallels between aging and end-stage renal disease, these two chapters are combined. Since the focus of this book is medical diseases of the kidney, the chapter on renal tumor has been deleted. Instead, an outstanding and most authoritative chapter on digital renal pathology is included.

We are deeply honored and grateful that a group of internationally acclaimed renal experts have joined us to present this information in an algorithmic, authoritative, concise, and yet comprehensive fashion. We thank them for their unrivaled scholarship and unmatched cooperation.

# Abbreviations

ACA	Affordable Care Act	CAD	computer-aided diagnostics
ACD	acquired cystic disease	CADI	chronic allograft damage index
ACE	angiotensin-converting enzyme	CAKUT	congenital anomalies of the kidney and urinary tract
ACL	anticardiolipin	CAN	chronic allograft nephropathy
ACR	American College of Rheumatology	CAP	College of American Pathologists
ADAS	autosomal dominant Alport syndrome	cAMP	cyclic adenosine monophosphate
ADPKD	autosomal dominant polycystic kidney disease	CBIR	Content Based Image Retrieval
ADTKD	autosomal dominant tubulointerstitial kidney disease	CCD	charged coupled device; cortical collecting duct
AKI	acute kidney injury	CD	collecting duct
AMPK	AMP-activated kinase	CD2AP	CD2-associated protein
ANA	antinuclear antibodies	CDK	cyclin-dependent kinase
ANCA	antineutrophil cytoplasmic antibodies	CFH	complement factor H
APCA	anticitrullinated peptide antibodies	CFTR	cystic fibrosis transmembrane conductance regulator
APIGN	acute postinfectious glomerulonephritis	CIC	circulating immune complex
APL	antiphospholipid antibody	CKD	chronic kidney disease
APOL-1	apolipoprotein L-1	CMOS	complementary metal oxide semiconductor
APRT	adenine phosphoribosyltransferase	CMV	cytomegalovirus
APS	antiphospholipid antibody syndrome	CNF	congenital nephrotic syndrome of the Finnish type
APSGN	acute poststreptococcal glomerulonephritis	CNI	calcineurin inhibitors
APSN	antiphospholipid syndrome nephropathy	CNS	congenital nephrotic syndrome
aPTT	activated partial thromboplastin time	CNT	connecting tubule
ARA	American Rheumatism Association	CNV	copy number variant
ARAS	autosomal recessive Alport syndrome	CBC	complete blood count
ARB	angiotensin receptor blocker	COX-2	cyclooxygenase-2
ARCD	acquired renal cystic disease	CRAB	hypercalcemia, renal failure, anemia, and bone lesions
ARPKD	autosomal recessive polycystic kidney disease	CRP	complement regulatory proteins
ART	anti-retroviral therapy	CT	computed tomography
AS	Alport syndrome	CTGF	connecting tubule glomerular feedback; connective tissue growth factor
ASO	antistreptolysin O	DAA	direct-acting antiviral
ATA	American Telemedicine Association	DAF	decay-accelerating factor
ATIN	acute tubulointerstitial nephritis	DC	dendritic cell
ATL	ascending thin limb	DCT	distal convoluted tubule
ATN	acute tubular necrosis	DDD	dense deposit disease
ATTR	transthyretin-associated	DGS	diabetic glomerulosclerosis
AVR	ascending vasa recta	DHA	dihydroxyadenine
AZA	azathioprine	DIC	disseminated intravascular coagulation
Bmp	bone morphogenetic protein	DILS	diffuse infiltrative lymphocytosis syndrome
BMT	bone marrow transplantation	DM	diabetes mellitus
Bp	blood pressure		
BSA	bovine serum albumin		
C1qN	C1q nephropathy		
C3GN	C3 glomerulonephritis		

List of Abbreviations

DMH	diffuse mesangial hypercellularity	IC	immune complex; intercalated cell
DMS	diffuse mesangial sclerosis	IE	infective endocarditis
DNP	diabetic nephropathy	IF	immunofluorescence
DSA	donor-specific antibody	IgA	immunoglobulin A
DTL	descending thin limb	IgAN	immunoglobulin A nephropathy
DVR	descending vasa recta	IgAV	IgA vasculitis
EBM	epidermal basement membrane	IHC	immunohistochemistry
EBV	Epstein–Barr virus	ILK	integrin-linked kinase
ECHO	Enteric Cytopathic Human Orphan	IMCD	inner medullary collecting duct
EDTA	ethylene diamine tetraacetic acid	IND	International Nomenclature of Disease
EGPA	eosinophilic granulomatosis with polyangiitis	INR	international normalized ratio
ELISA	enzyme-linked immunosorbent assay	IP	immunoperoxidase
eGFR	estimated glomerular filtration rate	IPS	interpodocyte space;
EM	electron microscopy		in-plane switching
EMP	endothelial microparticle	iPSC	induced pluripotent stem cell
ENA	extractable nuclear antigens	IRGN	infection-related GN
ER	endoplasmic reticulum	IRIS	immune reconstitution inflammatory syndrome
ESRD	end-stage renal disease	ISKDC	International Study of Kidney Diseases in Children
EULAR	European League Against Rheumatism	ISN	International Society of Nephrology
FDA	Food and Drug Administration	ITG	immunotactoid glomerulopathy
FDP	fibrin degradation products	IUGR	intrauterine growth restriction
FGF23	fibroblastic growth factor 23	IVIG	intravenous immunoglobulin
FMF	Familial Mediterranean fever	JG	juxtaglomerular
FSGS	focal segmental glomerulosclerosis	JGA	juxtaglomerular apparatus
GAG	glycosaminoglycan	JMS	Jones' methenamine silver
GBM	glomerular basement membrane	KDIGO	Kidney Disease: Improving Global Outcomes
GCK	glomerulocystic kidney	KDOQI	Kidney Disease Outcomes Quality Initiative
GCKD	glomerulocystic kidney disease	LA	lupus anticoagulant
GDNF	glial-derived neurotrophic factor	LAMP-2	lysosome-associated membrane protein 2
GFR	glomerular filtration rate	LCAT	lecithin cholesterol acyltransferase
GI	gastrointestinal	LCDD	light chain deposition disease
GINA	Genetic Information Nondiscrimination Act	LCKD	localized (or segmental) cystic kidney disease
GN	glomerulonephritis	LDL	low-density lipoprotein
GPA	granulomatosis with polyangiitis	LHCDD	light and heavy chain deposition disease
GSD	glycogen storage disease	LIS	laboratory information system
GUDMAP	Genitourinary Developmental Molecular Anatomy Project	LM	light microscopy
GVHD	graft versus host disease	LMWH	low molecular weight heparin
GWAS	genome-wide association study	LN	lupus nephritis
H&E	hematoxylin and eosin	LPHS	loin pain hematuria syndrome
HAART	highly active antiretroviral therapy	LPS	lipopolysaccharide
HBV	hepatitis B virus	LVH	left ventricular hypertrophy
HCDD	heavy chain deposition disease	LYVE-1	lymphatic endothelial hyaluronan receptor-1
HCV	hepatitis C virus	MAC	membrane attack complex
HDL	high-density lipoprotein	MAGUK	membrane-associated guanylate kinase
HELLP	hemolysis, elevated liver enzymes, and low platelets	MAP	mean arterial pressure
		MAPS	microangiopathic antiphospholipid-associated syndrome
HIF	hypoxia-inducible factor	MARP	million age-related population
HIV	human immunodeficiency virus	MBL	mannose-binding lectin
HIVAN	human immunodeficiency virus-associated nephropathy	MCD	minimal change disease
HSCT	hematopoietic stem cell transplant	MCTD	mixed connective tissue disease
HSP	Henoch–Schönlein purpura	MCP	membrane cofactor protein
HSPG	heparan sulfate proteoglycans	MD	macula densa
HTA	host targeting agent	MDRD	Modification of Diet in Renal Disease
HUS	hemolytic uremic syndrome	MEFV	Mediterranean fever (gene)
IBD	inflammatory bowel disease	MET	mesenchymal-to-epithelial transition

List of Abbreviations

MGRS	monoclonal gammopathy of renal significance	RMIC	renomedullary interstitial cell
MGUS	monoclonal gammopathy of undetermined significance	ROS	reactive oxygen species
MHC	major histocompatibility complex	RPGN	rapidly progressive glomerulonephritis
MIDD	monoclonal immunoglobulin deposition disease	RPS	Renal Pathology Society
MMF	mycophenolate mofetil	RRT	renal replacement therapy
MMP	metalloproteinase	RVT	renal vein thrombosis
MN	membranous nephropathy	SAA	serum amyloid A
MPGN	membranoproliferative glomerulonephritis	SD	slit diaphragm
MPO	myeloperoxidase	SEM	scanning electron microscopy
MRI	magnetic resonance imaging	SEP	subpodocyte exit pore
MSK	medullary sponge kidney	SLE	systemic lupus erythematosus
mTOR	mammalian target of rapamycin	SMA	smooth muscle actin
NA	Numerical Aperture	SNP	single nucleotide polymorphism
NAPlr	nephritis-associated plasmin receptor	SPEB	streptococcal pyrogenic exotoxin B
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies	SPNSG	Southwest Pediatric Nephrology Study Group
NCAM1	neural cell adhesion molecule	SPS	subpodocyte space
NCC	Na <sup>+</sup> Cl <sup>-</sup> cotransporter	SS	Sjogren's syndrome
NEP	neutral endopeptidase	STC	scattered tubular cell
NET	neutrophilic extracellular trap	STEC	Shiga toxin-producing <i>Escherichia coli</i>
NPSS	NEPTUNE pathology scoring system	STORM	stochastic optical reconstruction microscopy
nNOS	neuronal nitric oxide synthase	suPAR	soluble urokinase plasminogen activator receptor
NOS	not otherwise specified	SVR	sustained virologic remission
NPHP	nephronophthisis	SVV	small vessel vasculitis
NS	nephrotic syndrome; non-structural	TAL	thick ascending limb
NSAID	non-steroidal anti-inflammatory drug	TALH	thick ascending limbs of Henle
OMCD	outer medullary collecting duct	TA-P	time-average proteinuria
ORG	obesity-related glomerulopathy	TMA	thrombotic microangiopathy
PAN	polyarteritis nodosa	TBM	tubular basement membrane
PAS	periodic acid–Schiff	TBMN	thin basement membrane nephropathy
PCNA	proliferating cell nuclear antigen	TCC	terminal complement complex
PDGF	platelet-derived growth factor	TCR	T-cell receptor
PDGF-B	platelet-derived growth factor-B	TENS	transcutaneous electrical nerve stimulation
PDGF-RB	platelet-derived growth factor-B receptor	TG	transplant glomerulopathy
PEC	parietal epithelial cell	TGF	transforming growth factor
PHN	passive Heymann nephritis	TLR	Toll-like receptor
PKD	polycystic kidney disease	TM	thrombomodulin
PMN	polymorphonuclear leukocyte	TMA	thrombotic microangiopathy
PR	Peg-interferon and ribavirin	TNF	tumor necrosis factor
PRA	panel-reactive antibodies	TRI	tubuloreticular inclusion
PT	prothrombin time	TRU	tubuloreticular inclusion
PTC	peritubular capillaries	TSC	tuberous sclerosis complex
PT-BB	proximal tubular brush border	TTP	thrombotic thrombocytopenic purpura
PTH	parathyroid hormone	TTR	transthyretin
PTLD	posttransplant lymphoproliferative disorders	TWEAK	TNF-like weak inducer of apoptosis
PTMA	post-transplantation thrombotic microangiopathy	UB	ureteric bud
pVHL	von Hippel–Lindau protein	UPJ	ureteropelvic junction
RA	rheumatoid arthritis	USRDS	United States Renal Data System
RAAS	renin–angiotensin–aldosterone system	VDRL	Venereal Disease Research Laboratories
RAS	renin–angiotensin system	VEGF	vascular endothelial growth factor
RBC	red blood cell	VEGFA	vascular endothelial growth factor A
RCAD	renal cysts and diabetes	VHLD	von Hippel–Lindau disease
RCC	renal cell carcinoma	VLDL	very low-density lipoprotein
RF	rheumatoid factor	vWF	von Willebrand factor
		WM	Waldenstrom macroglobulinemia
		WRN	warfarin-related nephropathy
		WSI	whole-slide image
		XLAS	X-linked Alport syndrome