REVIEW

OPEN

The boundaries of normal kidney tissue for biomedical research

Jeffrey B. Hodgin[a,c], *Rajasree Menon*[b] *and Markus Bitzer*[c]

Purpose of review
In this review, we highlight the importance of understanding the inherent biological variability in normal kidney, or healthy reference tissue, to establish an accurate reference point for biomedical research. We explore this and the advantages and limitations of various sources of healthy reference tissue suitable for structural and omics-level studies.

Recent findings
Several large consortia are employing omic technologies for diseased and normal kidney tissue, underscoring the importance of utilizing healthy reference tissue in these studies. Emerging approaches, such as artificial intelligence and multiomic analyses, are expanding our understanding of structural and molecular heterogeneity in healthy reference kidney tissue and uncovering new insights.

Summary
Biological variability in healthy reference tissue at the functional, structural, and molecular level is complex and remains an active area of study. Thoughtful selection of healthy reference tissue sources is critical, providing the greatest potential for producing high-quality research outcomes.

Keywords
Aging kidney, healthy reference kidney tissue, nephrectomy, omics

INTRODUCTION

A normal kidney maintains the body's homeostasis, filters waste, balances electrolytes, and regulates blood pressure with a structure free from abnormalities, disease, or dysfunction. The "normal kidney", however, does not apply to most individuals with normal range kidney function as defined by KDIGO practice guidelines [1], due to significant biological variability. An understanding of the boundaries of the 'normal' kidney is crucial to understanding biological variability and providing an appropriate reference point, a healthy reference kidney, to identify and evaluate deviations caused by diseases, aging, or environmental factors. The challenge of defining a normal kidney carries significant implications in biomedical research, particularly in omics-level studies, where precise and clear definitions are critical. Thus, the normal kidney must be defined within ranges that consider biological variability. The sources of biological variability in 'normal' kidney tissues can arise from a range of factors, including the early developmental environment, sex and population differences, and perhaps most importantly, age-related changes (Fig. 1).

SOURCES OF VARIABILITY IN THE 'NORMAL' KIDNEY

Early developmental environment

Human nephrogenesis begins at approximately 9 weeks of gestation and concludes by 36 weeks. By full-term birth, the nephron count is fully established. However, autopsy studies have shown significant variability in nephron endowment, ranging from 210 000 to 2 700 000 nephrons per kidney, with an average of 600 000–800 000 [2–4]. Thus, there is no single

[a]Department of Pathology, [b]Department of Computational Medicine and Bioinformatics and [c]Department of Internal Medicine, Division of Nephrology, University of Michigan, Ann Arbor, Michigan, USA

Correspondence to Jeffrey B. Hodgin, MD, PhD, Associate Professor of Pathology and Medicine, University of Michigan, Ann Arbor, MI 48109, USA. Tel: +1 734 615 4233; e-mail: jhodgin@umich.edu

Curr Opin Nephrol Hypertens 2025, 34:218–223

DOI:10.1097/MNH.0000000000001069

KEY POINTS

- An understanding of the boundaries of the 'normal' kidney is crucial to understanding biological variability and providing an appropriate reference point, a healthy reference kidney, to identify and evaluate deviations caused by diseases, aging, or environmental factors.
- Sources of biological variability in the 'normal' kidney stem from differences in the early developmental environment, sex differences, and aging.
- The 'normal' kidney, or healthy reference tissue, has many subclinical macro and microstructural features, including nephron loss, increased global glomerulosclerosis, necessitating careful pathologic examination when selecting for reference tissue.
- Careful consideration of the source of healthy reference tissue (e.g. tumor nephrectomy, living kidney donor, etc.) is needed, as each has unique advantages and limitations.

'normal' nephron number. The timing of nephrogenesis cessation varies among individuals, typically occurring between 32 and 37 weeks of gestation, signaled by low birth weight or exposure to potential nephrotoxins in the perinatal period. These events may trigger adaptive changes that influence the structure and function of the kidneys later in life in apparently healthy individuals [5]. A lower nephron endowment is linked to a higher risk of developing conditions such as hypertension, chronic kidney disease (CKD), and cardiovascular disease later in life [6].

Sex differences

Sex differences in the healthy kidney are evident in terms of both function and structure as a result of influences of hormonal regulation, genetic factors, and developmental variations. Men have larger kidneys with higher cortical and medullary volumes, and nephron endowment, even after adjusting for body size [7▪]. In addition, women tend to maintain GFR better than men. Melsom *et al.* [8] investigated sex differences in the loss of kidney function in 1837 healthy individuals (53% women) and demonstrated a lower GFR in women than men at baseline aged 50–75 years, but a slower decline in mean GFR in women. The differences result in long-lasting effects on renal health with aging.

Population differences

The etiologies of the population differences in nephrosclerosis are of great consequence to public health but remain unknown. Seminal comparative studies by Richard Tracy across populations in the U.S., Peru, Bolivia, Mexico, Japan, and India revealed significant differences in nephrosclerosis, with emphasis on arteriosclerosis and arteriolohyalinosis, in autopsy series from normotensive patients across a wide range of ages [9–11].

The aging kidney

Aging in the kidney is a natural biological process marked by a progressive decline in cellular function and structural alterations. Age-related functional and structural changes have been a focus of research for decades, and in recent years, molecular analysis of the aging kidney has become increasingly important [12]. Due to a high metabolic demand and exposure to physiological stress, kidneys are particularly susceptible to an aging process that progressively impairs kidney resilience, adaptability, and increases susceptibility to CKD [13]. Notably, CKD has been viewed as a form of premature or accelerated aging

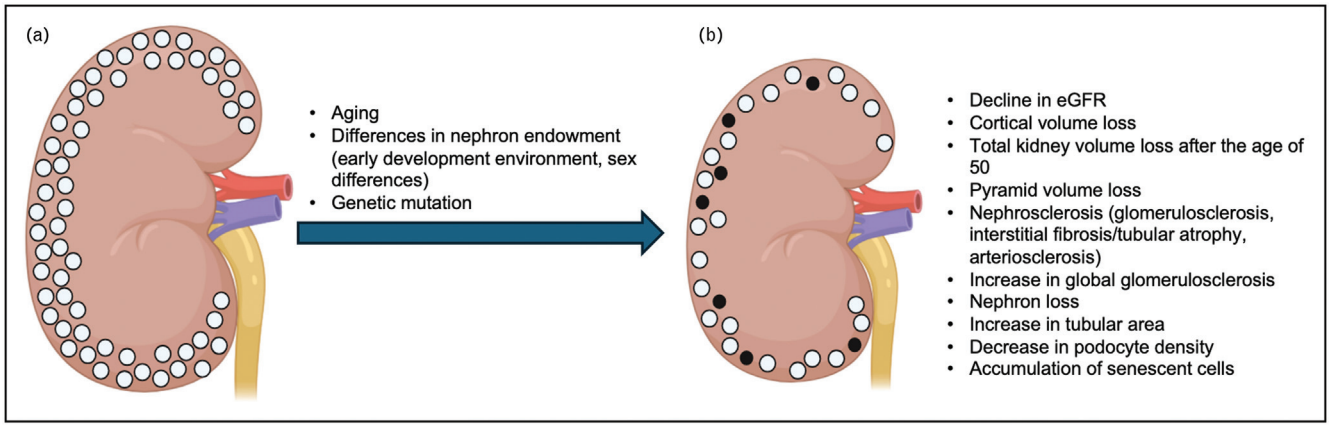

FIGURE 1. (a) Conditions that influence biological variability in the kidney and (b) the common functional, structural, and molecular changes that have been described. Shown are open (○) and globally sclerotic (●) glomeruli.

due to similar changes in morphology, function, and common underlying mechanisms [14].

Loss of renal function in the aging kidney

Healthy aging is consistently associated with a decline in glomerular filtration rate (GFR) by approximately 1 ml/min/1.73 m^2 annually beginning at age 30–40, with an accelerated drop after 60–70 years [15–17]. However, variability in GFR measurement methods complicates the interpretation and comparison of findings. In 1950, Davies *et al.* [18] documented a linear GFR reduction from age 30 to 90, averaging a 46% decline. Research involving living kidney donors has also confirmed age-related decreases in GFR, though the decline rates vary between 0.91 and 6.3 ml/min/1.73 m^2 per decade [19–22]. The large Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) reported a GFR decline of 0.95 ± 2.23 ml/min/1.73 m^2 annually among 1594 individuals aged 50–62 years [23]. This decline is attributed primarily to nephron loss, with renal hemodynamic changes, such as vasoconstriction and impaired endothelium-dependent vasodilation, also contributing [24–26]. Importantly, the distinction between physiological and pathological GFR decline is critical in older adults, as age-related reductions may naturally fall below the KDIGO CKD threshold of 60 ml/min/1.73 m^2, complicating the detection of kidney disease in the elderly.

Structural changes in the aging kidney

A study involving 1612 kidney donors used a novel deep-learning-based approach to demonstrate significant age-related declines in cortical volume, but not medullary volume, but after the age of 50, pronounced cortical atrophy leads to a noticeable reduction in total kidney volume [27,28]. Gregory *et al.* [29▪▪] demonstrated an age-related increase in pyramid volume and loss of pyramid number, likely reflecting pyramid merging with increased nephrosclerosis, using a deep-learning algorithm in CT images from 2876 living kidney donors. Undoubtedly, future studies will employ deep-learning approaches to discern additional age-related structural features. Microscopically, nephrosclerosis (glomerulosclerosis, interstitial fibrosis/tubular atrophy, and arteriosclerosis) and nephron loss are the major changes associated with healthy aging. In a study of 1203 living kidney donors, nephrosclerosis increased from 2.7% donors under age 30 to 73% among donors over age 70 [20]. A frequent and consistently described change is an age-dependent increase in focal global glomerulosclerosis in autopsy and living kidney donor studies, with half of nephrons lost over 50 years [3,20,30,31], primarily in the superficial cortex [32]. Valuable studies have established age-specific patterns of global glomerulosclerosis [33] and have proposed age-based thresholds for nephrosclerosis [34▪▪]. Nephron numbers decline with aging at an estimated rate of 6800 nephrons per kidney per year in autopsy studies [3,35]. However, the extent of nephron loss may be significantly underestimated when relying on the percentage of globally sclerosed glomeruli due to the eventual reabsorption of sclerosed glomeruli in older individuals [36]. Aging has also been associated with an increase in tubular area and cortical area per glomerulus [37], and to a decrease in podocyte density [38]. However, studies limited to healthy living kidney donors have not demonstrated a consistent increase in glomerular volume with age [36,37,39]. These findings suggest that while structural changes occur with aging, the relationship between nephron loss and glomerular volume remains complex and warrants further investigation.

Molecular changes in the aging kidney

Despite the well documented age-related structural and functional changes, the molecular mechanisms underlying the aging process are less clear. Several cellular and molecular mechanisms have been described to mediate aging-associated changes in the kidney. These complex mechanisms and their interplay with aging are extensively covered in excellent recent reviews [14,40,41▪,42▪]. In brief, the mechanisms that have been linked to mediate age-related changes in the kidney include accumulation of senescent cells, reduced autophagy, and genetic and epigenetic changes [41▪,43–45]. The senescence of renal cells is of particular interest because these cells secrete senescence-associated proteins that promote inflammation and fibrosis [46,47]. The relevance of any of these mechanisms has also been described in the setting of acute and CKD. Thus, molecular mechanisms and biological markers that are specific to the aging process in the kidney are lacking. The SenNet consortium [48] is funded to identify and characterize organ-specific markers for senescence cells and their findings are anxiously awaited by the kidney clinicians and research community.

SOURCES OF HEALTHY REFERENCE KIDNEY TISSUE FOR RESEARCH

Healthy reference kidney tissue serves as a critical baseline for assessing deviations in function, structure, and molecular or cellular profiles associated with disease states. Such reference tissue helps identify changes that may contribute to disease progression while enabling the characterization of natural variability in kidney structure and function.

Providing a standard for comparison also reduces the risk of false positives or negatives arising from artifacts or technical variability. However, different sources of healthy reference kidney tissue present unique benefits and constraints, requiring careful consideration of their suitability for specific research goals.

Nephrectomy

Kidney tissue from patients undergoing nephrectomies for malignant or benign tumors often includes unaffected areas of the kidney that have been a frequent source of healthy reference tissue for biomedical research. A general rule is to collect tissue at or more than 3 cm from the tumor to best avoid compression artifacts from the tumor on the uninvolved parenchyma. Nephrectomy samples allow access to tissue from a potentially large number of patients, with a broad age range, but without physical risk to patients. Additional benefits include the ability to collect a large portion of tissue in a controlled clinical setting, providing a wide range of sampling across the cortex and medulla. Studies have shown distinct molecular profiles across the cortex, medulla, and kidney papilla [49▪▪,50▪▪], and structural differences within the cortex, from superficial to deep, have been described [51▪▪]. Furthermore, analysis of large sections of the kidney cortex has revealed spatial heterogeneity of glomerular phenotypes that allows the detection of rare structural features such as atypical glomerular phenotypes [52▪]. On the other hand, kidney tissue from patients undergoing nephrectomy is enriched for patients with relevant comorbidities and risk factors of kidney disease, which could potentially cause disease-related structural and molecular changes [52▪]. Another concern with nephrectomy tissue is the potential impact of variable ischemia time during the surgical procedure, which may also impact molecular profiling. Importantly, a careful histopathologic review is needed for any source of healthy reference tissue to assess clinically silent pathology and determine suitability.

Autopsy

Kidneys obtained from autopsies have been extensively utilized in kidney research, particularly in studies examining kidney structure in aging populations and in large-scale studies investigating kidney health across diverse populations [3,35]. Autopsy tissue also offers full, unbiased access to the entire organ and enables detailed histological analyses of all kidney components providing comprehensive insights into normal and pathological structures, although structural analysis may be limited to chronic changes, such as glomerulosclerosis and interstitial fibrosis, due to variable autolysis in autopsy kidneys that mimics or obscures acute changes such as acute tubular necrosis. Notably, autopsies often reveal previously undiagnosed health conditions or exposures that impact kidney health [53]. Unfortunately, the quality of RNA, protein, and metabolites deteriorates rapidly after death, making the tissue unsuitable for molecular analysis. Employing a rapid autopsy program to minimize postmortem degradation may help to maintain tissue viability and molecular integrity [54].

Deceased donor

Kidneys unsuitable for transplantation, whether due to factors such as age, minor injury, or logistical constraints, are often utilized for research purposes with proper consent. Similar to autopsy specimens, deceased donor kidneys provide access to the entire organ, enabling sampling from multiple anatomical regions. These kidneys also reflect a wide range of ages, ethnicities, and health conditions, offering a diverse resource for research. However, the process, medical interventions prior to and the specific circumstances of the patient's death and the procurement process are highly variable and may subject deceased donor kidneys to diverse types of acute injuries, potentially affecting in particular molecular integrity.

Living donor

Living donor kidney tissue is a valuable source of healthy reference material for research. One significant benefit is that donors are extensively screened to confirm optimal kidney function and the absence of comorbidities. Additionally, tissue collection occurs under controlled conditions with prompt preservation, minimizing degradation and maintaining molecular integrity. However, the use of living donor tissue has limitations. The small tissue sample size constrains its application in large-scale studies involving multiple omic technologies. While pathological findings are minimal, obtaining additional tissue cores increases the risk of adverse events, such as bleeding, for the donor. Furthermore, the biopsies are usually performed after the kidney has been removed from the donor, perfused with special solutions *ex vivo* and reimplanted into the recipient, potentially introducing artificial changes that could alter the molecular profile.

Healthy volunteer

Kidney biopsies from healthy volunteers are a rare yet highly valuable resource for kidney research.

Similar to biopsies from living donors, these samples are limited by their small size but are likely the most suitable option for controls in studies involving tissue from patients with clinically evident diseases undergoing indication biopsies. Their procurement conditions closely match those of the disease samples, ensuring greater consistency, molecular integrity, and reliability for comparative analysis. The potential risks of complications from the kidney biopsy limit the number of samples that can be safely collected. Furthermore, the significant challenges associated with the recruitment of volunteers is a significant obstacle for this source of healthy kidney tissue, but it has been accomplished in a recent study investigating oxidative metabolism in the kidneys of young adults with type 1 diabetes [55▪].

CONCLUSION

In this review, we have highlighted the substantial biological variability inherent in the definition of a normal kidney and the varied sources of healthy reference tissue. One may consider a biopsy from a normotensive, average-weight individual, aged 20–25 years, to be ideal. However, even the definitions of normal blood pressure and body weight are controversial. What is required is careful consideration of the source of the healthy reference tissue within the context of the particular study or experiment. This is especially important for large consortia efforts such as the Kidney Precision Medicine Project [56], Human Biomolecular Atlas Project [57], Human Cell Atlas [58], and the Cellular Senescence Network [48], that apply multiomic characterization of the kidney. Such efforts also require sufficiently large sample numbers, with deep clinical and structural phenotyping, to efficiently assess thousands of molecular events. The effective utilization of healthy reference kidney tissue from diverse sources offers the best opportunity to achieve high-quality research outcomes.

Acknowledgements

None.

Financial support and sponsorship

J.B.H. is supported by NIH grants R01DK118431, U01DK114907, and R01AR080668 and Lupus Research Association, Global Team Science Award. M. B is supported by NIH grants R21DK126329, R03AG040651, CZF2019-002447, R01AG0799355, and U2CDK114886.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Group KDIGOKCW. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int 2024; 105(4S): S117–S314.
2. Keller G, Zimmer G, Mall G, *et al.* Nephron number in patients with primary hypertension. N Engl J Med 2003; 348:101–108.
3. Hoy WE, Douglas-Denton RN, Hughson MD, *et al.* A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. Kidney Int Suppl 2003; S31–S37.
4. Bertram JF, Douglas-Denton RN, Diouf B, *et al.* Human nephron number: implications for health and disease. Pediatr Nephrol 2011; 26:1529–1533.
5. Chevalier RL. Evolution, kidney development, and chronic kidney disease. Semin Cell Dev Biol 2019; 91:119–131.
6. Luyckx VA, Brenner BM. Clinical consequences of developmental programming of low nephron number. Anat Rec (Hoboken) 2020; 303:2613–2631.
7. ▪ Imberti B, Benigni A. Renal endowment in men and women: start from the beginning. Nephron 2024; 148:1–6.

Excellent mini-review covering nephron endowment in men and women.

8. Melsom T, Norvik JV, Enoksen IT, *et al.* Sex differences in age-related loss of kidney function. J Am Soc Nephrol 2022; 33:1891–1902.
9. Tracy RE, Lanjewar DN, Ghorpade KG, *et al.* Renovasculopathies in elderly normotensives of Bombay, India. Geriatr Nephrol Urol 1997; 7:101–109.
10. Tracy RE, Ishii T. What is 'nephrosclerosis'? lessons from the US, Japan, and Mexico. Nephrol Dial Transplant 2000; 15:1357–1366.
11. Tracy RE, Parra D, Eisaguirre W, Torres Balanza RA. Influence of arteriolar hyalinization on arterial intimal fibroplasia in the renal cortex of subjects in the United States, Peru, and Bolivia, applicable also to other populations. Am J Hypertens 2002; 15:1064–1073.
12. Jo MJ, Lee JK, Kim JE, Ko GJ. Molecular mechanisms associated with aging kidneys and future perspectives. Int J Mol Sci 2023; 24:16912–16929.
13. Zhang Y, Yu C, Li X. Kidney aging and chronic kidney disease. Int J Mol Sci 2024; 25:6585.
14. Tan H, Xu J, Liu Y. Ageing, cellular senescence and chronic kidney disease: experimental evidence. Curr Opin Nephrol Hypertens 2022; 31:235–243.
15. Delanaye P, Jager KJ, Bökenkamp A, *et al.* CKD: a call for an age-adapted definition. J Am Soc Nephrol 2019; 30:1785–1805.
16. Glassock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. Kidney Int 2012; 82:270–277.
17. Noronha IL, Santa-Catharina GP, Andrade L, *et al.* Glomerular filtration in the aging population. Front Med (Lausanne) 2022; 9:769329.
18. DAVIES DF, SHOCK NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J Clin Invest 1950; 29:496–507.
19. Poggio ED, Rule AD, Tanchanco R, *et al.* Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. Kidney Int 2009; 75:1079–1087.
20. Rule AD, Amer H, Cornell LD, *et al.* The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med 2010; 152:561–567.
21. Pottel H, Hoste L, Yayo E, Delanaye P. Glomerular filtration rate in healthy living potential kidney donors: a meta-analysis supporting the construction of the full age spectrum equation. Nephron 2017; 135:105–119.
22. Grewal GS, Blake GM. Reference data for 51Cr-EDTA measurements of the glomerular filtration rate derived from live kidney donors. Nucl Med Commun 2005; 26:61–65.
23. Eriksen BO, Stefansson VTN, Jenssen TG, *et al.* Elevated blood pressure is not associated with accelerated glomerular filtration rate decline in the general nondiabetic middle-aged population. Kidney Int 2016; 90:404–410.
24. Fliser D, Ritz E. Renal haemodynamics in the elderly. Nephrol Dial Transplant 1996; 11 Suppl 9:2–8.
25. Fliser D, Ritz E. Relationship between hypertension and renal function and its therapeutic implications in the elderly. Gerontology 1998; 44:123–131.
26. Higashi Y, Oshima T, Ozono R, *et al.* Aging and severity of hypertension attenuate endothelium-dependent renal vascular relaxation in humans. Hypertension 1997; 30:252–258.
27. Wang X, Vrtiska TJ, Avula RT, *et al.* Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. Kidney Int 2014; 85:677–685.

28. Korfiatis P, Denic A, Edwards ME, *et al.* Automated segmentation of kidney cortex and medulla in CT images: a multisite evaluation study. J Am Soc Nephrol 2022; 33:420–430.

29. ■■ Gregory AV, Denic A, Moustafa A, *et al.* The number and size of individual kidney medullary pyramids is associated with clinical characteristics, kidney biopsy findings, and CKD outcomes among kidney donors. J Am Soc Nephrol 2023; 34:1752–1763.

This large-scale study of 2876 participants employed a deep-learning algorithm on CT images of living kidney donors before donation, allowing associations of cortex volume, medullary volume, number of pyramids and pyramid volume with concurrent clinical chracteristics and kidney biopsy structural features.

30. Kaplan C, Pasternack B, Shah H, Gallo G. Age-related incidence of sclerotic glomeruli in human kidneys. Am J Pathol 1975; 80:227–234.

31. Denic A, Mathew J, Lerman LO, *et al.* Single-nephron glomerular filtration rate in healthy adults. N Engl J Med 2017; 376:2349–2357.

32. Denic A, Ricaurte L, Lopez CL, *et al.* Glomerular volume and glomerulosclerosis at different depths within the human kidney. J Am Soc Nephrol 2019; 30:1471–1480.

33. Kremers WK, Denic A, Lieske JC, *et al.* Distinguishing age-related from disease-related glomerulosclerosis on kidney biopsy: the Aging Kidney Anatomy study. Nephrol Dial Transplant 2015; 30:2034–2039.

34. ■■ Asghar MS, Denic A, Mullan AF, *et al.* Age-based versus young-adult thresholds for nephrosclerosis on kidney biopsy and prognostic implications for CKD. J Am Soc Nephrol 2023; 34:1421–1432.

Morphometric analyses of global glomerulosclerosis and interstitial fibrosis and tubular atrophy on 3020 living donors, 1363 tumor nephrectomy, and 314 patients with disease were used to define young-age thresholds and age-based thresholds by decade to better understand the risk of progressive chronic kidney disease when nephrosclerosis is abnormal for age.

35. McNamara BJ, Diouf B, Douglas-Denton RN, *et al.* A comparison of nephron number, glomerular volume and kidney weight in Senegalese Africans and African Americans. Nephrol Dial Transplant 2010; 25:1514–1520.

36. Denic A, Lieske JC, Chakkera HA, *et al.* The substantial loss of nephrons in healthy human kidneys with aging. J Am Soc Nephrol 2017; 28:313–320.

37. Denic A, Alexander MP, Kaushik V, *et al.* Detection and clinical patterns of nephron hypertrophy and nephrosclerosis among apparently healthy adults. Am J Kidney Dis 2016; 68:58–67.

38. Hodgin JB, Bitzer M, Wickman L, *et al.* Glomerular aging and focal global glomerulosclerosis: a podometric perspective. J Am Soc Nephrol 2015; 26:3162–3178.

39. Tan JC, Busque S, Workeneh B, *et al.* Effects of aging on glomerular function and number in living kidney donors. Kidney Int 2010; 78:686–692.

40. Fang Y, Gong AY, Haller ST, *et al.* The ageing kidney: molecular mechanisms and clinical implications. Ageing Res Rev 2020; 63:101151.

41. ■ Rex N, Melk A, Schmitt R. Cellular senescence and kidney aging. Clin Sci (Lond) 2023; 137:1805–1821.

Comprehensive review of current knowledge on cellular senescence and the aging kidney.

42. ■ Shankland SJ, Rule AD, Kutz JN, *et al.* Podocyte senescence and aging. Kidney360 2023; 4:1784–1793.

A focus on senescence in the aging podocyte.

43. Tang C, Livingston MJ, Liu Z, Dong Z. Autophagy in kidney homeostasis and disease. Nat Rev Nephrol 2020; 16:489–508.

44. Rowland J, Akbarov A, Eales J, *et al.* Uncovering genetic mechanisms of kidney aging through transcriptomics, genomics, and epigenomics. Kidney Int 2019; 95:624–635.

45. Liu F, Chen J, Li Z, Meng X. Recent advances in epigenetics of age-related kidney diseases. Genes (Basel) 2022; 13:.

46. Baar MP, Brandt RMC, Putavet DA, *et al.* Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell 2017; 169:132–147; e16.

47. Baker DJ, Childs BG, Durik M, *et al.* Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 2016; 530:184–189.

48. Consortium S. NIH SenNet Consortium to map senescent cells throughout the human lifespan to understand physiological health. Nat Aging 2022; 2:1090–1100.

49. ■■ Haug S, Muthusamy S, Li Y, *et al.* Multiomic analysis of human kidney tissue identified medulla-specific gene expression patterns. Kidney Int 2024; 105:293–311.

Gene expression (RNA-seq), chromatin assembly (ATAC-seq), chromatin conformation (Hi-C), and spatial transcriptomic were used to molecularly characterize the human kidney cortex and medulla and find unique insights into the function and development of the medulla.

50. ■■ Canela VH, Bowen WS, Ferreira RM, *et al.* A spatially anchored transcriptomic atlas of the human kidney papilla identifies significant immune injury in patients with stone disease. Nat Commun 2023; 14:4140.

Using single-cell/nucleus transcriptomics and spatial transcriptomics in normal and diseased kidneys, the authors define a spatial molecular landscape and molecular pathways in disease.

51. ■■ Denic A, Gaddam M, Moustafa A, *et al.* Tubular and glomerular size by cortex depth as predictor of progressive CKD after radical nephrectomy for tumor. J Am Soc Nephrol 2023; 34:1535–1545.

Morphometric analysis of glomeruli and proximal and distal tubules, from 1367 tumor nephrectomies, separately in the superficial, middle, and deep cortex revealed glomerular volume in the middle and deep cortex and distal tubular diameter predicted CKD.

52. ■ Schaub JA, O'Connor CL, Dailey M, *et al.* Spatial heterogeneity of glomerular phenotypes affects kidney biopsy findings. Kidney360 2023; 4:1598–1607.

Morphologic analysis of globally sclerotic, segmentally sclerotic, ischemic-like, and imploding glomeruli from tumor nephrectomies revealed clustering of atypical glomeruli and likely underdetection of atypical glomerular phenotypes from biopsies that do not capture subcapsular areas.

53. Perrone ME, Chang A, Henriksen KJ. Medical renal diseases are frequent but often unrecognized in adult autopsies. Mod Pathol 2018; 31:365–373.

54. Hooper JE. Rapid autopsy programs and research support: the pre and post-COVID-19 environments. AJSP Rev Rep 2021; 26:100–107.

55. ■ Choi YJ, Richard G, Zhang G, *et al.* Attenuated kidney oxidative metabolism in young adults with type 1 diabetes. J Clin Invest 2024; 134:.

In this study, kidney biopsies from 20 healthy volunteers were used in comparison to young adults with type 1 diabetes to analyze metabolic signatures from proximal tubules.

56. de Boer IH, Alpers CE, Azeloglu EU, *et al.* Rationale and design of the Kidney Precision Medicine Project. Kidney Int 2021; 99:498–510.

57. Consortium H. The human body at cellular resolution: the NIH Human Biomolecular Atlas Program. Nature 2019; 574:187–192.

58. Regev A, Teichmann SA, Lander ES, *et al.* The human cell atlas. Elife 2017; 6: e27041.

