Chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is defined by persistent urinary abnormalities or impaired excretory renal function. While progression to end stage kidney disease (ESKD) is a concern, the majority of those with CKD are at risk for accelerated cardiovascular disease and death. For those that do reach ESKD the limited accessibility to kidney replacement therapy is a problem in many locations worldwide.. Risk factors for CKD include low nephron number at birth and nephron loss due to increasing age or acute and chronic kidney injuries. For example, the pandemic of obesity and type 2 diabetes largely accounts for the increasing global prevalence of CKD and there is an increasing awareness of genetic causes for CKD and accelerated CKD progression. The management of CKD is focused on early detection or prevention, treatment of the root cause if possible, and attention to secondary processes which contribute to ongoing nephron loss, i.e. remnant nephron hyperfiltration. Blood pressure control and inhibition of the renin-angiotensin system are the corner stones of therapy. CKD complications such as CKD complications such as anemia, metabolic acidosis, and secondary hyperparathyroidism impact cardiovascular health, as well as quality of life, and so require diagnosis and therapy. Primary prevention of CKD, early diagnosis, and secondary prevention of CKD progression are needed to reduce cardiovascular disease, CKD-related morbidity, and to prevent ESKD, whether or not kidney replacement therapies are available.

[H1] Introduction

Chronic kidney disease (CKD) is a syndrome defined as persistent alterations in kidney structure, function or both with implications for health [1]. Examples of structural abnormalities include cysts, tumors, malformations or atrophy, which become evident by imaging. By contrast, kidney dysfunction can become evident as hypertension, edema, growth delay in children, and changes in output or quality of urine; these changes are most often recognized by increased serum levels of creatinine, cystatin C or blood urea nitrogen. The most common pathological manifestation,

regardless of the initiating insult or disease, of CKD is some form of renal fibrosis.

The Kidney Disease Improving Global Outcomes (KDIGO) initiative classifies an individual as having CKD if abnormalities of kidney structure or function persist for >3 months. KDIGO describes a classification system based on severity, into numerous stages of CKD using a two dimensional matrix based on estimated or measured glomerular filtration rate (eGFR, mGFR) and on extent of albuminuria (FIG. 1) [1]. Primary care settings often do not assess albuminuria but proteinuria via dip stick analysis, but dip stick +, ++, and +++ usually approximates with the three albuminuria stages. GFR and albuminuria/proteinuria are used to classify CKD because GFR is a well-established marker of renal excretory function and albuminuria is an indicator of renal barrier dysfunction, i.e. glomerular injury. Both have found to be reliable predictors of long term CKD outcomes

As the kidney is formed by many independent functional and anatomical 'units', the nephrons GFR, can be expressed by the equation: $GFR_{(Total)} = GFR_{(single\ nephron)} \times$ number of nephrons. This implies that when the number of nephrons declines, total GFR will not change as long as single nephrons can increase their individual GFR (known as single-nephron GFR (SNGFR). Vice versa, a decline in total GFR implies a significant loss of nephrons with remnant nephrons probably operating at their maximum possible SNGFR. That is, CKD can be thought of generally as a loss of functional nephrons but usually represents loss in nephron number. Furthermore, the KDIGO stages are derived from large databases of general, high risk and nephrology populations. The categories define risk of progression to ESKD that is defined as G5 (GFR <15 mL/min/1.73 $m^{2)}$ and a number of other outcomes including risk of cardiovascular disease (CVD), death, AKI, infections, and hospitalizations. The KDIGO staging has proven to be very instrumental in decision making on patient management.

Whether CKD should be diagnosed and staged using absolute thresholds irrespective of age remains controversial [2, 3]. The mGFR in healthy adults aged 20-40 years is about 107 ml/min/1.73 m^2 and declines at a rate of about 0.7 ml/min/1.73 m^2 per year [4, 5]. By age 75 years, many otherwise healthy individuals (without significant co-morbidity) will have lost

50% of their nephrons and their GFR that was present at age 25 years [6]. A substantial number of older healthy individuals have eGFR <60 ml/min/1.73 m^2 and no abnormal albuminuria (KDIGO CKD G3a A1) meeting the KDIGO criteria for CKD albeit having only a small increase in relative risk of all-cause mortality [7, 8]. The threshold of GFR that should be used to detect CKD in younger persons is equally controversial [9]. The upper and lower limits for mGFR in a 25 year old healthy person being considered as a living kidney donor is about 136 to 78 ml/min/1.73 m^2 respectively [5]; some have suggested that a threshold of <75 ml/min/1.73 m^2 would be more appropriate for young adults, and values below this threshold are associated with a significantly increased relative risk of all-cause mortality and ESKD [10].

The etiology of the impaired kidney function is important, and thus in addition to classifying the severity of CKD by GFR and albumin levels, understanding the risk factors or causes of CKD is essential (Box 1), and recommended by the guidelines [1]. In this Primer, we discuss the global prevalence of CKD, the different diseases underlying poor nephron endowment or nephron loss, the pathophysiology of CKD progression, the diagnosis, screening, and prevention of CKD, and CKD management to improve outcomes and quality of life. Finally, we name several research domains potentially offering improvements for CKD management in the near future.

[H1] Epidemiology

Rates of age-standardized death and disability due to most non-communicable diseases have decreased over the past 20 years, but such favourable trends are not present for CKD. The Global Burden of Disease study reports indicate an increase burden of CKD (with substantial worldwide variation) to which diabetes mellitus seems to be the most important contributor [11-13]. CKD as a cause of mortality has increases over the last 25 years from 21st to 13th', and now contributes 1.35% of the global burden of disability life years lost, growing at a rate of 1% per annum [11, 13, 14]. Note that most prevalence data are based on levels of GFR only, without consideration of albuminuria, based on the first CKD classification system reported in 2002.

[H2] Prevalence

CKD stage G3–5 prevalence in adults varies worldwide, with values reported as 1.7% in China [15], 3.1% in Canada [16], 5.8% in Australia [17] and 6.7% in the USA [18]. In Europe the range is slightly narrower: from 2.3% in Germany [19], 2.4% in Finland [20], 4.0% in Spain [20] to 5.2% in England [21]. Such numbers should be viewed with caution because they are often based on a single eGFR assessment (that is not considering the actual definition, which includes the factor of time (present for >3 mo; thus it is possible that positive "CKD cases" may overestimate the true prevalence of CKD [22]. The epidemiology of CKD in low and middle-income countries (LMICs) is poorly characterized due to the lack of community-based studies, inconsistent assessment of kidney function and non-standardized or non-calibrated approaches[23]. Nevertheless, in South-East Asia, some Latin American countries (such as Mexico) and in sub-Saharan Africa, when assessed, the prevalence of CKD appears to be consistent with the estimates of 10-16% [23-25].

[H2] Risk factors

CKD is more common in people over 65 but the probability of progression to ESKD is higher in younger people with CKD, albeit sometimes over long period of times [26]. Interestingly,while the prevalence of CKD is higher in women than in men, men are more likely to progress to ESKD [26]. The most common underlying diseases are diabetes mellitus and hypertension, particularly in in high and middle income countries. In those with diabetes, CKD prevalence is estimated in 30- 40%. Whether this is due to diabetes per se or due to microvascular disease is not known. However, in LMICs, CKD is often due to infectious diseases and glomerulonephritis (a group of diseases that lead to inflammation of the glomerulus) [27]. Current and future changes in socio-economic circumstances and population age distributions will increase the absolute number of people with CKD in these countries, where numbers of elderly persons are rising, and with increasing diabetes and obesity epidemic, may change the cause of CKD in those populations as well. Furthermore, low birth weight is associated

150 with CKD later in life; the global risks of preterm birth and low birth weight are around 10% and 15%,
151 respectively. Thus, millions of children are born at risk of CKD later in life and are found at the lower
152 percentile of age-matched GFR [28, 29]. Specific populations are at higher risk for CKD, in part due to
153 genetic factors, and others due to interaction of genetic and environmental factors. Those groups at
154 higher risk include, in alphabetical order: Aboriginal Australians, African Americans, Hispanics,
155 indigenous populations in Canada, South Asians, Oriental Asians, and Pacific Islanders.

156 Endemic forms of CKD suggest regional triggers, which are often difficult to define among
157 potential candidates such as specific infections, toxins, behaviours or climate-related factors [30].
158 Reports of chronic interstitial nephritis or CKD of undetermined origin (CKDu) in sugar cane and other
159 agricultural workers in Latin America, Sri Lanka, India, and more recently in Cameroon, Mexico, and
160 Australia, are examples of this [30-32].

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162 [H2] Children

163 Little is known about CKD in children because of the absence of registries, and that they are not
164 included in many clinical studies. In Europe, the 2014 incidence of paediatric ESKD was 5.7 per million
165 age-related population (pmarp) in children aged 0-14 years and the prevalence 32.2 pmarp [33]. Earlier
166 estimates suggested the incidence and prevalence were 8.3 pmarp and 58 pmarp, respectively, in
167 children aged 0-19 years [34], which is lower than 14.7 pmarp and 103.9 pmarp for the age group 0-21
168 years in the United States [35]. In high income countries, congenital disorders are responsible for the
169 majority of cases of paediatric CKD; by contrast, in acquired causes, such as infection and glomerular
170 diseases, predominate in LMICs [36].

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172 [H2] Kidney replacement

173 Understanding the information on kidney replacement therapy in the context of CKD is important for
174 identifying gaps and focusing on solutions to those gaps [37]. Often countries do not know the number
175 of patients with prevalent CKD but do have information on dialysis numbers. Given that not all

people progress to ESKD, estimates of those with CKD can be extrapolated; conversely if CKD rates are known then numbers on dialysis can reveal inequities in availability of dialysis. Data on the incidence of kidney replacement therapy for ESKD can only be obtained from countries with dialysis registries. Data are missing in particular from LMICs, where such registries do not exist. In 2014, incidence of kidney replacement therapy varied from 49 per million population (pmp) in Bangladesh to as high as 455 pmp in Taiwan [38]. The majority of patients started kidney replacement therapy on dialysis, because pre-emptive transplantation as an initial modality is not freely available. Kidney transplant rates differed substantially by country from 1 pmp in Bangladesh to 60 pmp in Jalisco (Mexico). There was also huge variation in the prevalence of kidney replacement therapy (FIG. 2): from 113 pmp in Bangladesh to 3,219 pmp in Taiwan [38].

In many European countries, more than half of all kidney replacement therapy patients are transplant recipients [38]. This is in contrast to the situation in some Asian countries like Taiwan, Japan and the Philippines where kidney transplantation is hardly performed [38]. There are multiple reasons why transplantation is not available despite the availability of expensive dialysis services: cultural, socioeconomic and health care infrastructure deficiencies (lack of biopsy services, lack of surgeons, lack of immunology laboratories) account for many of these. Existence of available dialysis and transplant services has not been systematically documented; however the Global Kidney Health Atlas [38; full report at *www.theisn.org*] describes availability of kidney replacement therapy worldwide. Note that the registry data for dialysis and transplantation described above does not reflect the true need for kidney replacement therapy, which may account for the wide variability in incidence and prevalence. Estimates of unmet need vary from 2 to 7 million people per year [39]. Note that availability and accessibility are not the same, and even when services ae available in a country or region, not all individuals may have access to them (depending on cost reimbursement, demand, and specific policies).

[H1]Mechanisms/pathophysiology

[H2] Nephron loss and compensation

In humans, nephrons are generated from the 12th-36th week of gestation with a mean number of 950,000 per kidney in a range from approximately 200,000 to >2.5 million [40]. No new nephrons can form upon injury and, during growth from childhood to adulthood, the available nephrons increase in size to accommodate increased renal demands. However, as people age, GFR declines (FIG. 3). Although nephrons can deal with transient increases in filtration load (such as upon food and fluid intake) by transient increases in SNGFR ("renal reserve") [41, 42], longer or persistent increases in body mass (for example, during pregnancy or obesity) promote nephron hypertrophy as the compensatory mechanism. Any injury- (or kidney donation-)related nephron loss may have the same effect (FIG. 4). Indeed, either severe kidney injury or combinations of injury with ageing-related nephron losses — especially in individuals with poor nephron endowment and/or obesity — accelerates persistent increased SNGFR and loss of remnant nephrons[43].

Remnant nephron hypertrophy is triggered by persistent elevations of SNGFR and filtration pressure (that is, glomerular hypertension) across the glomerular filtration barrier, which implies glomerular hyperfiltration. Specifically, glomerular hyperfiltration and hypertension together promote the release of tumour growth factor-alpha/epithelial growth factor receptor [44, 45], leading to nephron hypertrophy that reduces glomerular hypertension by increasing filtration surface [46]. Indeed, increased SNGFR and remnant nephron hypertrophy allows kidney donors to maintain an apparently "normal" renal function, despite lacking 50% of nephrons. Obviously, kidney donation does not necessarily cause CKD progression when donors are carefully selected for good nephron endowment, the absence of obesity, diabetes, and ongoing nephron injury [47, 48]. However, in other circumstances, hyperfiltration-driven increases in glomerular dimensions can potentially be harmful [42, 46, 49-51]. Beyond a certain threshold of hypertrophy, increasing podocyte (which are key octopus-shaped cells that maintain the glomerular filtration barrier of the nephron shear stress promotes

podocyte detachment, focal segmental glomerulosclerosis (FSGS, a pathological entity in which renal injury results in sclerotic lesions in segments of glomeruli), global glomerulosclerosis and subsequent nephron atrophy, a vicious cycle further reducing nephron number and the SNGFR of remnant nephrons (FIG. 5) [44, 46,52-55].

[H2] Impaired glomerular filtration and fibrosis

Persistent podocyte hypertrophy and glomerular hyperfiltration, maintained by angiotensin II production, ultimately aggravate podocyte loss and proteinuria, eventually impacting on glomerular filtration Angiotensin-II, a peptide hormone that is part of the renin-angiotensin system (RAS) and drives vasoconstriction and aldosterone secretion (and thus sodium retention and an increase of blood pressure) directly impairs the glomerular barrier sieving function, possibly via inhibiting expression of the podocyte protein nephrin, a structural component of the slit diaphragm necessary for maintaining the glomerular filtration barrierindependently of its hemodynamic effects [56]. Angiotensin-II possibly also contributes to the dysregulated response of parietal epithelial cell precursors along Bowman`s capsule, generating FSGS lesions instead of replacing lost podocytes [57]. This structural remodelling of the glomerular tuft barrier presents clinically as proteinuria. Proteinuria not only serves as a marker for nephron damage but also predicts CKD progression [44, 58, 59]. Mechanistically, albuminuria also impairs the capacity of parietal epithelial cells to regenerate podocytes [44], instead further promoting the formation of FSGS lesions (FIG. 5) [60, 61].

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CKD progression also involves non-specific wound healing responses including interstitial fibrosis. Albuminuria and complement, and infiltrating immune cells activate proximal tubular epithelial cells to induce the secretion of and pro-fibrotic mediators followed by interstitial inflammation and fibrosis [62]. Interstitial fibrosis is frequently considered as an additional factor driving further nephron injury, e.g. via promoting renal ischemia [62] but, as in other organs, scar formation may also be essential to mechanically stabilize the remaining nephrons [63]. The increased tubular transport

workload of remnant nephrons also involves anaerobic metabolism, intracellular acidosis, and endoplasmic reticulum stress — all promoting secondary tubular cell injury [44, 60].

[H2]Risk factors

Several factors can contribute to the pathogenesis of CKD, including low birth weight, pregnancy, obesity, diabetes, and ageing. Each of these scenarios contributes different factors that lead to and/or exacerbate nephron loss, promoting the cycles of injury and ultimately resulting in kidney failure.

[H3]Prematurity and low birth weight.

Newborns with low birth weight (owing to preterm birth or intrauterine growth restriction) frequently display incomplete kidney development [64-66]. Depending on the severity of prematurity, poor nephron endowment can cause either early childhood CKD or CKD later in life [64-70]. The associated risk was estimated among US adolescents for every 13 individuals born at low birth weight, one had reduced GFR and one had raised systolic blood pressure, and this risk increases with age [29]. The risk of low birth weight infants (<2599 g) to experience CKD up to the age of 17 is fourfold increased compared to infants with a birth weight of >2500 g (FIG.3B) [69]. CKD onset at puberty is common in these individuals when rapid body growth exceeds the capacity of nephron number to accommodate the increasing filtration load[71]. In milder cases, poor nephron endowment at birth promotes the development of hypertension, CKD later in adults or a faster progression of glomerulonephritis to ESKD (FIG.3C) [29, 66, 70, 72, 73]. All of these factors increase the risk of cardiovascular disease.

[H3]Genetic factors.

Congenital abnormalities of the kidney and the urinary tract (CAKUT) are the most common congenital abnormalities [74]. CAKUT present a wide spectrum of causes for kidney hypodysplasia,

imparting low nephron number and risk of CKD later in life[75, 76]. Genetic testing has revealed that ~20% of early-onset CKD (defined as CKD manifesting before 25 years of age) cases can be attributed to a monogenic cause [77]. Beyond CAKUT, these conditions include ciliopathies, cystic kidney diseases, tubulopathies, and podocytopathies causing FSGS [75-78].

Until recently, monogenic causes of CKD were mostly reported in children or adolescents, but genetic variants also contribute as co-factors to CKD progression in adults (FIG. 4). For example, an *UMOD* gene variant, present on 17% of the alleles in the general population, is associated with CKD [79-81]. Another example is gene variants of apolipoprotein L1 (*APOL1*) in African Americans, which confer resistance to *Trypanosoma brucei* infections in sub-Saharan Africa [82]. However, these variants affect endosomal trafficking and autophagic flux, which ultimately leads to podocyte loss, glomerulosclerosis, nephron loss, and CKD progression [83, 84]. This may explain faster CKD progression in many patients with sub-Saharan ancestry [82].

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[H3]Obesity.

A larger glomerular size on mildly obese (BMI>30 and <35) but otherwise healthy individuals suggests an increased SNGFR [85]. In general, the association between obesity and poorer renal outcomes persists even after adjustments for higher blood pressure and diabetes mellitus, suggesting that obesity-driven glomerular hyperfiltration directly contributes to nephron loss [86, 87]. Severe obesity alone or moderate obesity in combination with other factors such as genetic, low nephron number or aging can lead to development of proteinuria, secondary FSGS, and progressive CKD (FIG. 4) [86, 88-91].

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[H3]Pregnancy.

The latter trimester of pregnancy involves volume expansion (that is, an increase in blood volume) causing an increase of total GFR by 50% [92], implying a respective increase of SNGFR. These physiological adaptations are transient and without consequences in women with normal nephron number. However, in women with low nephron endowment or previous injury-related CKD (such as

in women with lupus nephritis), pregnancy-related glomerular hyperfiltration exacerbates remnant nephron glomerular hyperfiltration and hypertrophy. In some patients, final trimester pregnancy-related glomerular hyperfiltration then passes the threshold of compensation and triggers rapid CKD progression presenting with proteinuria and hypertension — a condition known as eclampsia. Pre-existing CKD G3A2 or higher, obesity, excessive body weight increase during pregnancy are well-known risk-factors for eclampsia [93].

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[H3]Diabetes.

Diabetes is a well-known condition associated with massive glomerular hyperfiltration, evident from increased total GFR and renomegaly [51]. Hyperglycemia promotes the sodium-glucose transporter (SGLT)-2-driven reabsorption of sodium in the proximal tubule, a process that subsequently inactivates tubuloglomerular feedback and activates the RAS at the *macula densa* [94, 95]. The result is induction of a permanent dilation of the afferent arteriole and vasoconstriction of the efferent arteriole — permanently increasing SNGFR and total GFR [96].

Although diabetes-driven glomerular hyperfiltration can be compensated for many years in younger patients with normal nephron number, it serves as a drastic accelerator single nephron hyperfiltration such as patients with low nephron endowment, injury- or ageing-related nephron loss, obesity or those who are pregnant [97]. Unfortunately, this is a highly prevalent combination of risk factors in older patients with type 2 diabetes, for which dual SGLT2/RAS inhibition can elicit potent nephroprotective effects [98].

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[H3]Acute kidney injury.

Acute kidney injury (AKI) is a clinical syndrome defined by an acute deterioration of renal function resulting in the accumulation of metabolic waste and toxins, subsequent uremic complications, and potentially failure of other organs [99]. AKI is highly prevalent in hospitalized patients and can imply irreversible losses in nephron number[100]. In Western countries AKI occurs in both outpatient and

inpatient settings, the latter of which is simpler to document, and has been the focus of multiple papers describing the phenomenon and aiding in the understanding of the strong association between AKI and CKD. The causes of non hopsital/institutuion-based AKI are diarrhea, infections, dehydration, medications, while in hospital it can be attributed to these same factors and exposures to nephrotoxins (dye) and is mostly observed in patients with multiple morbidities [101]. By contrast, in LMICs and tropical countries, AKI occurs frequently outside the hospital setting following episodes of diarrhoea, infections and obstetric complications [102]. Nephrotoxins can also cause AKI-related nephron loss inside and outside hospitals; for example, neonates treated with aminoglycosides, cancer patients receiving chemotherapy or communities exposed to environmental toxins such as heavy metals or aristolochic acid can experience AKI episodes [30].

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[H3]Ageing.

The slope of GFR decline varies among individuals depending upon age (FIG. 3), genetic factors, blood pressure, diseases implying kidney injury and body weight. Histologically, kidney ageing presents as global glomerulosclerosis, the respective atrophy of entire nephrons, and subsequent interstitial fibrosis [53, 85]. Whether ageing-related nephron loss is associated with hypertrophy (and glomerular hyperfiltration) of remnant nephrons is not consistently reported in the literature [53, 85], but the analytical difficulties on how to precisely assess nephron number, glomerular volume, and how to acknowledge the different functions of juxtamedullary versus cortical nephrons can affect the interpretation of such data [53, 85]. Ageing is associated with decreasing podocyte density and total numbers [53]. Endomitosis-related mitotic catastrophe and podocyte detachment may contribute to glomerulosclerosis[53, 103,104].

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[H2]Systemic effects

The kidney is involved in multiple complex hormonal processes important in anemia, bone integrity, in regulation of acid base and electrolyte homeostasis, as well as blood pressure control

through neuroendocrine and volume sensors. As nephron mass declines, patients will suffer from complications associated with dysregulation of many of these systems. Anemia, vitamin D deficiency, hyperparathyroidism, acidosis, hyperkalemia and hyperphosphatemia, hyperuricemia, as well as hypertension and expansion of effective circulating fluid volume are all clinical manifestations of these derangements. Interestingly, they do not occur in all individuals at the same point in the progressive loss of kidney function, and there are some maintain excellent tubular/ excretory function despite derangements in hormonal function (i.e. severe anemia, and normal electrolytes). Not all of the derangements are symptomatic, and the severity of the symptoms is variable between individuals. They include: disorders of fluid and electrolytes, mineral and bone disorder, anemia, hypertension, dyslipidemia, endocrine abnormalities, in children growth impairment, decreased clearance of renally excreted substances from the body (eg, hyperuricemia), metabolic acidosis. Related symptoms may be fatigue, anorexia, weight loss, pruritis, nausea, vomiting, muscle cramping, edema, shortness of breath, to name a few. None are specific for CKD.

[H3] Fluid and electrolyte abnormalities.

Sodium and water balance — Sodium and intravascular volume balance are usually maintained via homeostatic mechanisms until the GFR falls below 10 to 15 mL/min per 1.73 m^2. However, the patient with mild to moderate CKD, despite being in relative volume balance, is less able to respond to rapid infusions of sodium and is, therefore, prone to fluid overload. In some cases, especially with an acute water load, hyponatremia and hypertension may occur as a consequence of fluid retention. Some patients, such as those with nephronophthisis and some with obstructive uropathy, have an impaired ability to concentrate urine, and have symptoms of polyuria. These children are at risk for hypovolemia, as they will continue to have large urine losses even when they are volume depleted.

Hyperkalemia — In children with CKD, hyperkalemia develops due to reduced GFR causing inadequate potassium excretion. Also, potassium excretion is dependent upon an exchange with sodium at the distal tubule. A low GFR decreases delivery of sodium to this site where there is

reduction in the exchange rate with potassium into the urinary lumen. Other contributory factors for hyperkalemia include: high dietary potassium intake, catabolic conditions with increased tissue breakdown, metabolic acidosis, secondary type IV renal tubular acidosis (RTA) in some patients with obstructive uropathy, decreased renin production by the juxtaglomerular apparatus, primary or secondary hypoaldosteronism related to RAS inhibitor-related impaired cellular uptake of potassium

[H3]Metabolic acidosis.

Metabolic acidosis is observed in patients with advanced CKD and is related to the fall in total ammonium excretion that occurs when the GFR decreases to below 40 to 50 mL/min per 1.73 m^2 (GFR category G3). In addition, there is a reduction in both titratable acid excretion (primarily as phosphate) and bicarbonate reabsorption. As the patient approaches ESKD, the serum bicarbonate concentration tends to stabilize between 12 and 20 mEq/L. A level <10 mEq/L is unusual, as buffering of the retained hydrogen ions by various body buffers prevents a progressive fall in the bicarbonate concentration. In children with CKD, metabolic acidosis has a negative impact on growth.

[H3] Anemia.

The anemia of CKD is due primarily to reduced renal erythropoietin production. The anemia of CKD is principally normocytic and normochromic. By comparison, the finding of microcytosis may reflect iron deficiency or aluminum excess, while macrocytosis may be associated with vitamin B12 or folate deficiency. If left untreated, the anemia of CKD is associated with fatigue, weakness, decreased attentiveness, increased somnolence, and poor exercise tolerance.

[H3]Mineral bone disease.

Chronic kidney disease-mineral and bone disorder (CKD-MBD) presents as a broad clinical spectrum encompassing abnormalities in mineral metabolism, bone structure, and extraskeletal calcifications

that are found with progressive CKD. Patients with mild CKD (G2 KDIGO) may have reduced serum

calcidiol and/or calcitriol levels, and an elevated serum parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) level [105]. Patients with more advanced CKD-MBD have bone pain, difficulty in walking, and/or skeletal deformities and a higher risk of fracture [106].

[H3]Hypertension.

Hypertension can be present in the earliest stages of CKD, and its prevalence increases with progressive declines in GFR. Hypertension is high in children with CKD, ranging from 54 to 70 percent of patients [107]. Hypertension is due to activation of the RAS and volume expansion. In some cases, hypertension arises from corticosteroids or calcineurin inhibitors such as cyclosporine or tacrolimus used to treat the underlying kidney disease.

[H3]Dyslipidemia.

Abnormal lipid metabolism is common in patients with CKD and is one of the primary factors that increase the risk for CVD.

[H3]Hyperuricemia.

Elevated uric acid levels may develop in patients with CKD due to decreased urinary excretion. Serum uric acid greater than 7.5 mg/dL is an independent risk factor for accelerated progression of CKD and should be treated to have a better outcome.

[H3]Cardiovascular disease.

CVD is the leading cause of death in patients with CKD worldwide [14]. The increased incidence of CVD is due to the high prevalence of CVD risk factors, such as hypertension, dyslipidemia, hyperuricemia, abnormal glucose metabolism obesity. Young adults (25 to 34 years) with CKD have at least a 100-fold higher risk for CVD-related mortality compared with the general population [108]. Patients with a

435 glomerular etiology of CKD and proteinuria were more likely to have CVD risk factors. The CKD-

related cardiovascular alterations resemble all aspects of an accelerated ageing process associated with a shortening of relative telomere length [109]. The vasculature can be affected by both, atherosclerosis and arteriosclerosis, with lipid-rich plaques but also abundant media calcification. The burden of atherosclerotic CVD increases in the early stages of CKD, and the burden of non-atherosclerotic CVD increases in the more advanced stages of CKD. The „two“ diseases involve different factors that cause distinct changes in the risk factor profile and contribute differently to outcomes during the course of CKD. Adaptive changes of the heart include left ventricular hypertrophy (LVH) but also dilatation with subsequent both, systolic and diastolic dysfunction. There are two different patterns of LVH: concentric LVH, which occurs in the presence of hypertension, and eccentric LVH, which is associated with volume overload and anemia. Early and sustained induction of fibroblast growth factor-23 was recently discovered as a driver of LVH in CKD [110].

The absolute risk of cardiovascular events in individuals with pre-dialysis CKD is similar to that of patients with established coronary artery disease in the general population [111], and the increase in risk multifactorial: a higher prevalence of insulin resistance [112], high blood pressure, vascular calcification [113, 114], inflammation and protein-energy wasting [115]. ESKD is associated with a range of metabolic abnormalities, the so-called milieu of uremic toxicity [116], activation of the neuro-hormonal axis [117], vitamin D receptors [113], that may all contribute to accelerated ageing of the vasculature and damage to the heart. Hemodialysis itself may have a direct negative effect on the heart, so-called myocardial stunning [118]. As a consequence the cardiac and vascular mortality are several times higher in patients with low GFR or on dialysis than in the general population. Thus, the risk of CVD in patients who require dialysis depends largely on their cardiovascular health at dialysis initiation. In patients with healthy arteries, the pre-dialysis management strategy should be continued to prevent new cardiovascular lesions. Consequently, risk factors for CVD should be managed intensively in the pre-dialysis period, during transition, and at dialysis initiation.

[H3]Endocrine dysfunction.

In patients with CKD, the following endocrine systems become dysfunctional as kidney function progressively deteriorates. Each of these is discussed in greater detail separately. There are abnormalities in gonadal hormones in both male and female patients, which can results in reduced fertility and sexual problems. In children, these abnornalities result in delayed puberty in two-thirds of adolescents with ESKD [119]. End-organ resistance to GH due to increased levels of insulin growth factor binding proteins appears to play a major role in growth impairment in children with CKD [120]. Abnormalities in thyroid function can also be observed.

[H3]Neurological signs.

Uremia is associated with cognitive alterations ijn adults and lower performance in all neurocognitive domains development in children. The neurologic findings can range from seizures and severe intellectual disability to subtle deficits.

[H3]Sleep and fatigue.

Daytime sleepiness and fatigue are common and increase with decreasing kidney function. Sleep disorders (restless leg syndrome/paroxysmal leg movements, sleep-disordered breathing, excessive daytime sleepiness, and insomnia) are also common

[H3]Uremia.

The onset of ESKD (ie, GFR category G5) results in a constellation of signs and symptoms referred to as uremia. Manifestations of the uremic state include anorexia, nausea, vomiting, growth retardation, peripheral neuropathy, and central nervous system abnormalities ranging from loss of concentration and lethargy to seizures, coma, and death. Patients who are uremic also have an increased tendency to bleed secondary to abnormal platelet adhesion and aggregation properties. Pericardial disease (pericarditis and pericardial effusion) is an indication to institute dialysis. The initiation of RRT should be considered

[H1] Diagnosis, screening and prevention

The clinical presentation of CKD depends upon the underlying disorder and the severity of renal impairment. Patients with early stages of CKD G1-2 are usually asymptomatic. From CKD G3-5 patients may experience weakness related to anemia and polyuria. Only in late stages and in untreated patients symptoms may include anorexia, vomiting, weakness, and fatigue, which are referred to as symptoms of uremia.

[H2]Detection and diagnosis

CKD can be detected during a periodic health assessment in an asymptomatic person or during evaluation of individuals at risk for CKD (Box 1); as a consequence of the incidental finding of abnormal laboratory values in connection with an acute or chronic illness; during an investigation of symptoms and/or signs relating to the kidneys or urinary tract (such as haematuria); or during discovery of abnormal laboratory values in a population-based screening program. Importantly, the two biochemical parameters (GFR and proteinuria) used in the aforementioned KDIGO matrix[1] define and classify a "generic" form of CKD, and adding an etiological diagnosis is both highly desirable and recommended by KDIGO (The **C**ause/**G**FR/**A**lbuminuria [CGA] classifications system), whenever possible, such that the underlying conditions can be treated first to halt progression of CKD. Progression is defined according to changes in eGFR by KDIGO[1]. Several tests can be performed to confirm a CKD diagnosis and identify its cause. It must be stressed that a diagnosis of CKD, according to the KDIGO construct, requires persistence or progression of the defining abnormality for at least 3 months. A single value of GFR or albuminuria is insufficient and if used for diagnosis of CKD will lead

[H3] Measuring and estimating GFR.

First, the assessment begins with measurement of serum creatinine concentration (under steady-state conditions) and applying formulas for estimated GFR (eGFR – creatinine, like CKD-EPI eGFR-

creatinine). It must be recognized that the results of these creatinine based tests can be influenced by changes in muscle bulk (atrophy or hypertrophy), dietary intake of cooked red meat (strict vegan diet) and alterations in tubular secretion of creatinine from exposure to drugs (e.g. trimethoprim-sulfamethoxazole) [121, 122]. Alternative approaches using serum cystatin_C concentrations have also been proposed. While not influenced by muscled bulk and diet, the cystatin C -based formulas for eGFR can be affected by inflammation, obesity, thyroid disease, diabetes, and steroid administration [123]. Second, some eGFR formulashave not been extensively validated in older subjects and may not apply to Asians or Africans [124, 125]. Third, the requirements for inclusion of demographic variables of age and gender, to correct for differences in creatinine generation, may also create unwanted complications in determining prognostic implications of a calculated GFR . Newer eGFR formulas such as FAS (full age spectrum) or CKD-EPI using serum creatinine, cystatin C or a combination or Cystatin C or a combination of both have improved accuracy to predict mGFR [126, 127]. Although cumbersome and expensive, mGFR assessments using urinary clearance methodology can sometimes be needed, but applying methods of plasma clearance of Iohexol or of radiolabelled Iothalamate could avoid some of these issues. In well-defined circumstances, such as stratifying long term risks of uni-nephrectomy for potential living kidney donors, such studies can be useful [128, 129]. As mentioned in the introduction, caution should be exercised in using a fixed and arbitrary threshold of <60ml/min/1.73m2 of GFR alone (in the absence of abnormal proteinuria or imaging) for the diagnosis of CKD in older or elderly adults. A GFR of 45-59ml/min/1.73m2 is fairly common in otherwise healthy seniors, depending on their age, due to the normal physiologic loss of nephrons and GFR with organ senescence [130].

533533

[H3]Measuring proteinuria.

Abnormal rates of urinary excretion of albumin or total protein are essential for detection of CKD when GFR is normal and contribute to the assessment of prognosis [131]. Proteinuria (or albuminuria) can be determined in multiple ways, including simple “dip stick” qualitative methods,

point-of-care urinary albumin concentration tests, random un-timed urine samples for calculation of urine protein (or albumin) to creatinine ratios (UPCR or UACR in mg/mg or mg/mmol), or timed 24 hour urine collections and measuring absolute protein or albumin excretion [132, 133]. Each of these has advantages and pitfalls. But it is important to recognise that not all patients with CKD have abnormal urinary protein excretion. For example, early in the course of Autosomal Dominant Polycystic Kidney Disease the urinary protein exertion is normal only slightly increased [134].

Urinary protein or albumin excretion is more variable than serum creatinine levels, and can be influenced by posture, activity, fever or drugs so multiple specimens must be collected to enhance reliability. UPCR and UACR methods can be influenced by the prevailing urinary creatinine excretion rate; i.e. low creatinine excretion (from sarcopenia) can increase UPCR or UACR values even at normal absolute protein or albumin excretion rates. Hence, adjusting for the effect of urinary creatinine excretion can enhance the accuracy of UPCR and UACR measurements [132, 133].

In the KDIGO schema, UACR values are divided into three categories [1], namely, normal or low, which is <30 mg/g creatinine (<3.0 mg/mmol, formerly "normo-albuminuria"); moderately increased, which is ≥30-299 mg/g creatinine (>3.0-29 mg/mmol, formerly "micro-albuminuria"); and severely increased, which is ≥300 mg/g creatinine (30 mg/mmol, formerly "macro-albuminuria"). Even with a normal eGFR, CKD can be diagnosed with persistent UACR of >30 mg/g creatinine. Each incremental increase in UACR is associated with an increased risk of mortality and ESKD, so sustained albuminuria (or proteinuria) is a powerful prognostic marker.

The corresponding "dipstick" (urinalysis test strip) values (and protein concentration in mg/dL) are negative (<10 mg/dL) to trace (10-15 mg/dL) for normal, 1+ (30 mg/dL) for moderate and 2+ (>100 mg/dL) or greater for severe proteinuria. Persistent proteinuria of >1+ is a good predictor of a tendency for CKD progression, i.e. GFR decline of > 5 ml/min/1.73 m^2/year or 7 times the normal rate of loss with ageing [135]. Thus, albuminuria or proteinuria allow early detection of CKD (see Screening below), but several forms of progressive CKD can present with normal or only slightly increased albumin or protein excretion, especially tubulo-interstitial diseases such as autosomal

564 dominant polycystic kidney disease [134]. Marked proteinuria (in excess of 3.5 g/d in and adult),
565 especially when accompanied by a reduction in serum albumin concentration (referred to as
566 “nephrotic syndrome”) nearly always implies a diagnosis of a primary or secondary glomerulopathy
567 underlying CKD [136].

568568

569 [H3]Biopsy and pathology.

570 Percutaneous kidney biopsy is a very valuable tool in assessement of the underlying cause for CKD.
571 The indications for performance of a renal biopsy in a patient with CKD depends upon the benefits to
572 be obtained (precise diagnosis, better prognosis, appropriate therapy) and the risks of a biopsy-
573 related complications. Kidney biopsies are commonly recommended for adult patients with
574 nephrotic syndrome (urine protein excretion of >3.5 g/d and serum albumin levels <3.5 g/dL) but
575 may also be indicated for evaluation of unexplained rapidly progressive loss of kidney function,
576 persistent hematuria and low-grade- proteinuria (0.5-3 g/d), of even isolated proteinuria (1-3 g/d) [137].
577 Depending on the circumstances leading to the procedure, the pathologic findings can vary widely,
578 but in states of marked proteinuria glomerular diseases are most likely be seen. The degree of
579 tubule-interstitial scarring can provide useful prognostic information. The risks of renal biopsy are
580 minimal in experienced hands, and complications are mostly related to post-biopsy bleeding. Fatal
581 complications are rare (about 1;20,000). Major complications, such as nephrectomy or transfusion
582 requiring bleeding are more common (about 1:250-500) [138, 139].

583583

584 [H3]Other tests.

585 Continuing advances in the field of serum and urine proteomics, microRNA biology and in serology
586 are providing many new powerful and non-invasive tools to identify specific diseases or groups of
587 diseases that may revolutionize the approach to detecting and diagnosing CKD in the future [140].
588 These new tools may also expand the horizon of prognosis into new areas beyond GFR and
589 proteinuria estimation — giving rise to exciting new possibilities for “precision” medicine whereby

care of CKD is personalized based diagnostic and prognostic characteristics. Unfortunately, many patients with CKD are only recognized in the later stage of the disease (Categories G3B-G5) where CKD complications such anemia, metabolic acidosis, mineral-bone disease provide additional diagnostic clues.

In addition, both detection and diagnosis of CKD, also rely on renal imaging (ultrasonography, CT and MRI), careful examination of the urinary sediment, and specialized biochemical and serologic tests suitable to detect specific disorders causing CKD (Box 2). Imaging tests are particularly valuable as they provide information on kidney size, contours, location, and density as well as anatomy of the urinary drainage system (pelvis, ureters and bladder). Specific lesions, such as cysts, dilation of ureters or pelvis, calcification, masses, scars an provide valuable clues to the cause of CKD or even generate a specific diagnosis (such as autosomal dominant polycystic kidney disease or obstructive uropathy) [141]. Then urine sediment examination is important for the detection and quantification of haematuria, leukocyturia and casts.

Genetic testing is also emerging as an important tool for diagnosing CKD, particularly in children or young adults. Autosomal dominant polycystic kidney disease, podocytopathies causing steroid-resistant nephrotic syndrome, Fabry's disease, Alport syndrome, are other well-known entities requiring a genetic diagnosis. Using next-generation sequencing displays an unexpected genetic heterogeneity and alterations in numerous different genes in a significant proportion of not only familial or syndromic patients but also in sporadic cases of CKD. These observations imply the need for updating the current management in terms of diagnostic algorithms and therapeutic choices [77, 142].

[H2]Screening

In the context of CKD, screening can take two forms: population screening, for example, using "dipstick" urinary testing of school children or soldiers; or "opportunistic screening", whereby

616 physician encounters for other medical reasons can be used to screen for CKD. Population-based
617 screening can be further divided into general population screening or "targeted" screening of high-
618 risk population groups (such as diabetic or family members related to subjects with diagnosed CKD).
619 Unfortunately, the benefits and harms of both forms of screening for CKD have not been rigorously
620 tested in long-term prospective studies, so the overall benefits and harms of population-based
621 screening for CKD are poorly understood and further trials are needed [143, 144]. Population-based
622 screening for CKD is not recommended by the United States Preventive Task Force largely due to
623 insufficient evidence of benefit (or harm) [145]. Evidence in favor of case-finding (i.e., testing for CKD in
624 people with recognized risk factors, such as hypertension or diabetes) is slightly better, but still
625 incomplete. Accordingly, the American College of Physicians determined that current evidence was
626 insufficient to evaluate the benefits (or harms) of screening and case-finding for CKD [146]. The position
627 on screening for CKD varies widely around the world, with several countries having long-established
628 programs (Japan and Singapore for example) and others that have introduced them as part of
629 universal health care systems systems (The United Kingdom for example) [147-151].

630 Both screening and case-finding for CKD are logistically hampered by the need for re-
631 evaluation at a defined interval to fulfil the duration requirement for diagnosis. Therefore, one-off
632 testing using eGFR or proteinuria has a high "false positive" detection/diagnosis rate, and possible
633 misclassification of subjects by use of a fixed (non-age-sensitive) eGFR thresholds, as discussed. The
634 potential harms of general population screening involve excessive follow-up diagnostic procedures,
635 unnecessary referral of subjects erroneously diagnosed as having CKD, the anxiety induced by being
636 labelled as having CKD, and potential impact on insurability. Nevertheless, several national kidney
637 organizations advocate screening for CKD. Monte Carlo simulations support case-finding strategies in
638 diabetic subjects for albuminuria or hypertension [152], because early treatment may offer significant
639 effects on delaying CKD progression and ESKD [153]. Some studies have suggested that testing for
640 abnormal albuminuria may be an efficient way of stratifying populations for more intensive search
641 for modifiable risk factors for CKD and cardio-vascular events, such as hypertension and diabetes [154].

Indeed, abnormal proteinuria (even only slightly above the upper limit of normal) identifies people at greater risk for ESKD and/or cardiovascular morbidity and mortality [155]. As mentioned before, population screening for CKD using eGFR tends to substantially over-diagnose CKD in older subjects with no or minimal proteinuria. Opportunistic testing for CKD has much merit, especially if the subjects have other risk factors such as diabetes, hypertension, or a family history of CKD. In such patients an eGFR should be assessed along with an estimate of albuminuria or total protein excretion ("dipstick"), UACR or UPCR- adjusted for creatinine excretion rate). It also must be appreciated that older subjects with CKD G3 (as defined by KDIGO, see above) detected in screening programs or otherwise in primary care practices tend to have a rather benign prognosis, at least over the short term of 5 years or less. Shardlow et al found a very low rate of ESKD (0.2%) and stable or remission of CKD was found in 53% of such subjects (average age 73 years at entry) after 5 years of follow-up [156].

Finally, there are a few special circumstances where testing of apparently healthy individuals for CKD may be indicated. For example, first degree relatives of a patient with autosomal-dominant polycystic kidney disease (ADPKD) are eligible for screening with renal ultrasound or MRI regardless of results of eGFR or proteinuria. Siblings of patients with Fabry's disease, Alport syndrome, or thin basement membrane nephropathy might also benefit from genetic analysis as well. African-Americans with hypertension or HIV infection may receive more informed prognosis by assessment of *APOL1* risk alleles, but population-based screening for *APOL1* risk alleles is not yet justifiable [157]

[H2]Prevention

From a societal perspective, prevention of CKD is preferable to after- the-fact treatment of kidney disease at its end-stage by dialysis or transplantation. Both primary prevention (occurring before CKD is established) and secondary prevention (initiated to slow the rate of CKD progression or to affect the associated co-morbidities or complications; see below, Management) should be considered.

Primary prevention attacks the root causes of CKD and includes mitigating exposures to

668 nephrotoxic agents and events (Box 1). Reduction of the burden of infectious diseases (such as HIV,
669 Malaria, *Streptococcus* infection) have already yielded some protection from CKD, but many
670 challenges remain. Preventing obesity and the associated type 2 diabetes mellitus is a global
671 challenge [158]. The discovery of a central role for sugar and fructose intake and metabolism in obesity
672 can be cited as an example of progress with implications for primary prevention. Indeed, better
673 glycemic control may also eventually prevent CKD and its progression [153, 159-161]. Improved recognition
674 and reduction of the prevalence of AKI may also have dividends on prevention of CKD, especially in
675 counties where AKI is common, under-recognized and under-treated such as equatorial Africa. Given
676 the importance of low nephron endowment, fetal malnutrition and/or dysmaturity and manifested
677 by low birth weight, global efforts to reduce fetal malnutrition and dysmaturity should have
678 enormous "pay-back" in later years and focussed effects are beginning to address this important
679 topic [66].

680680

681 [H1] Management

682 Several aspects need to be considered when managing patients with CKD: controlling nephron injury,
683 normalizing single nephron hyperfiltration, controlling CKD-related complications, and preparing the
684 patient for kidney replacement therapy. At the core of these is the principle of 'the earlier-the
685 better', which is the effort to reduce the progression to ESKD and optimize renal outcomes.

686 The impact of early therapy is well documented for Alport syndrome [162]. Initiating RAS
687 blockade based on the genetic diagnosis before any signs of kidney disease can have dramatic effects
688 on renal outcomes, whereas initiating RAS blockade as late as CKD G3 only somewhat delayed ESKD
689 (FIG. 6) [162]. Further support comes from a posthoc analysis of clinical trials testing RAS blockade in
690 diabetic kidney disease. The effect on gaining ESKD-free years was highest when RAS blockade was
691 initiated at the time of microalbuminuria and lowest when initiated once a diagnosis of CKD G3 or G4
692 was made [163]. Therefore, early diagnosis and treatment are essential to prevent nephron loss from as
693 early as possible.

694694

695 [H2]Controlling ongoing nephron injury

696 Nephron injury can be driven numerous triggers (Table 1), and abrogating these triggers will slow
697 progression to CKD and ESKD. For example, genetic abnormalities can cause CKD either by fostering
698 nephrocalcinosis [164], cystic degeneration or by weakening epithelial integrity such as in genetic
699 podocytopathies or in abnormal processing or storage of metabolites or glycoproteins [78, 165]. Specific
700 cures for genetic kidney diseases exist in some forms and are mostly limited to enzyme replacement
701 therapy or substrate supplementation (Table 1). The genetic basis of immune-mediated nephron
702 injury is not yet fully explored but C3 glomerulonephritis or atypical hemolytic uremic syndrome
703 (aHUS) can be controlled with complement inhibitors, an area of intense and promising research [166].
704 Most acute forms of immune-mediated nephron injury present either as vasculitis, immune complex
705 glomerulonephritis or interstitial nephritis (including allograft rejection). These disorders can often
706 be targeted with immunomodulatory drugs (and sometimes with plasma exchange) to limit nephron
707 loss from attack by the humoral and/or cellular elements of the immune system [167].

708 In contrast, in smoldering immune injury, such as in chronic IgA nephropathy, it is difficult to
709 dissect CKD progression driven by immune versus non-immune mechanisms and the efficacy of
710 immunosuppression versus RAS blockade and blood pressure control is less evident [168]. Kidney biopsy
711 may establish the diagnosis and can also guide management by assessing the ongoing activity of
712 immune injury versus irreversible damage, e.g. in lupus nephritis, IgA nephropathy or allograft
713 dysfunction. Specific treatments are also available for CKD related to urinary tract obstruction,
714 infections, and some forms of toxic injury (Table 1). However, even upon complete abrogation of the
715715 injurious trigger, recovery of lost nephrons is impossible.

716716

717 [H3]Preventing any avoidable injury of remnant nephrons.

718 Avoiding further episodes of AKI is crucial to minimize stress on the remnant nephrons in CKD
719 kidneys. This implies patient education on avoidable nephrotoxins such as radio contrast media,

NSAIDs, certain antibiotics or other endemic or occupational toxins. Hypovolemic states as well as urinary outflow obstruction should be avoided. Additionally, not every asymptomatic leukocyturia implies bacterial infection and antibiotic treatment should be limited to the presence of dysuria, bacteriuria, and leukocyturia. Smoking cessation is essential minimize CVD [169].

[H2] Normalizing single nephron hyperfiltration

Rigorous RAS inhibition with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has the capacity to substantially reduce SNGFR and glomerular filtration pressure, which leads to a decline in not only proteinuria but also total GFR — and, hence, moderately increases serum creatinine levels [170]. At first, this serum creatinine increase is worrisome to patients (and physicians) and requires clarification that reducing hyperfiltration in remnant nephrons is the central strategy to retard CKD progression in patients with proteinuria. In contrast, ACEi or ARBs do not retard the progression of non-proteinuric forms of CKD such as ADPKD but still may have benefits on the associated cardiovascular complications [171]. ACEi or ARBs should be titrated to the maximal possible dose, while hyperkalemia can be corrected using loop diuretics or potassium-binding resins [172]. A moderate increase in serum creatinine levels indicates a decline in SNGFR, which is a powerful predictor of the intended nephroprotective effect [173]. Numerous RCTs have documented the class effect of RAS inhibitors to retard or even halt CKD progression [44]. Reducing dietary salt and drugs that support control of blood pressure and hyperlipidemia, often referred to as “remission clinic protocol”, may further reduce proteinuria and retard CKD progression [174, 175]. Such interventions are affordable and are of importance where kidney replacement therapy is not available or affordable.

Avoiding or correcting obesity can also reduce filtration load and glomerular hypertension; hence, a normal BMI is a treatment target to retard CKD progression [176]. Any immunosuppression-related benefit of using steroids in CKD may be counterbalanced by steroid-related obesity that drives glomerular hyperfiltration and secondary FSGS, which could explain why steroid treatment falls short in retarding progression of IgA nephropathy-related CKD [168]. Finally, concomitant diabetes

has important implications for CKD management [177]. Hyperglycemia maximizes glomerular hyperfiltration via SGLT2-driven vasodilation of the afferent arteriole of the remnant nephrons, which cannot be controlled by RAS inhibitors [94]. Recently, SGLT2 inhibitors have been shown to reverse this process and elicit profound additive nephroprotective effects on CKD progression [98, 178]. Their capacity to also reduce CVD (in patients with type 2 diabetes) [178, 179] provides a strong rationale for dual RAS/SGLT2 blockade in patients with diabetes and CKD.

[H2]Controlling CKD complications

CKD is associated with a number of secondary complications that require management (Box 3), the most relevant of which in terms of overall mortality is CVD [14]. Cardiac and vascular alterations also arise from endocrine failure (e.g. lack of erythropoietin, vitamin D, parathyroid hormone), which causes anemia and secondary hyperparathyroidism [180]. Myocardial fibrosis is the final consequence of the multiple underlying causes.

Large randomized controlled trials in patients on hemodialysis have tested a number of different interventions intended to reduce cardiovascular events such as dialysis dose and flux, erythropoietin-stimulating agents, statins, RAS blockade, folic acid, cinacalcet or vitamin D derivatives but have largely been unsuccessful [181-183]. For example, statins may prevent cardiovascular events in patients on dialysis, but the magnitude of any relative reduction in risk is substantially smaller as compared to what can be achieved in CKD 2-4 [183-186]. For example, reduction of LDL cholesterol with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events more efficiently in patients with CKD G2-4 than with CKD G5 or 5D [183]. Hence, early intervention with standard-of-care is essential in patients with CKD 2-4. In parallel, similar concepts for cardiovascular protection are administered for progression of diabetic and non-diabetic kidney disease. For these patients, guideline-directed approaches to achieve target blood pressure through administration of RAS blockers, salt restriction and anemia prevention is the mainstay of therapy [187,

[188]. Guidance is also available for the correction of acidosis and mineral and bone metabolism disorders (Box 3) [189].

[H2]Preparing for kidney replacement therapy

ESKD typically requires renal replacement therapy, although conservative treatment is a potential alternative option, especially in older adults with limited life span. Counseling on the options (kidney transplant, hemodialysis, peritoneal dialysis or no dialysis) should be coordinated by the nephrologist and involve a multidisciplinary team including the general practitioner. Early counseling is essential because informed patients are better prepared to face kidney failure. Indeed, late referral, i.e. at the time of ESKD, is associated with worse health status at the time of kidney replacement therapy initiation, higher mortality after starting dialysis, and decreased access to transplant [190]. However, one of the biggest challenges nephrologists face is to predict kidney disease progression, which does not follow a steady linear decline. This unpredictability often becomes a barrier to timely shared decision making between patients and physicians and could lead to adverse patient outcomes [190], and may offset the relationship between the early pre-dialysis nephrology care for adults with late stage of CKD and improved outcomes [191]. KDIGO suggested that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive-impairment [1]. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73m^2. Moreover, living donor preemptive renal transplantation in adults should be considered when the GFR is <20 ml/min/1.73m^2, and there is evidence of progressive and irreversible CKD over the preceding 6-12 months [1].

[H3]Hemodialysis.

In 1945 Willem Kolff was the first to successfully treat kidney failure of a patient by performing

hemodialys using an artificial kidney able to clear blood from uremic toxins [192]. Since then numerous technical innovations have optimized the procedure that meanwhile has become available (but not everywhere affordable) all over the world [38]. Preparing patients for hemodialysis involves referral for vascular access placement. The types of access include arteriovenous fistulae, arteriovenous grafts and central venous catheters (which are for short-term use) (FIG. 7A-C); arteriovenous access is the preferred option for hemodialysis, although there is no consensus about the optimal timing for creation, especially for arteriovenous fistulae [193]. To protect the blood vessels for permanent vascular access, attention should be taken to avoid venous puncture or intravenous catheter placement proximal to the wrist, which implies that venous puncture at the back of the hand still being possible. Arteriovenous access (either fistulae or grafts) is associated with better outcomes than central venous catheters [194] [195]. Patients with a central venous catheter have poorer survival than those who subsequently convert to functional arteriovenous access [196]. Thus, a functional arteriovenous access is preferable for all patients in which the vascular status allows to install a fistula.

[H3]Peritoneal dialysis.

Peritoneal dialysis is another way to eliminate uremic toxins from the blood using the peritoneal membrane as an exchange interface. For this a transcutaneous catheter is implanted into the peritoneal cavity that allows repetitive daily drainage and refills of dialysate fluid. After some hours of reaching equilibrium between uremic blood and fresh dialysate each dwell is expected to drain excess fluid, metabolic waste products including uremic toxins (FIG. 7D). There are published guidelines regarding insertion and perioperative management of peritoneal dialysis catheters. A peritoneal dialysis catheter may be ready for use after 2 to 3 weeks. However, there is marked variability in peritoneal dialysis catheter insertion techniques (open surgery, blind via trocar or blind via Seldinger technique) and perioperative management [197]. Interestingly, patients starting on peritoneal dialysis show better initial outcome and preservation of residual renal function, especially in the first 2 years as compared to patients on hemodialysis [198].

823823

[H3]Kidney transplantation.

When available, suitability for kidney transplantation should be evaluated according to age and co-morbidities, but it may take months to complete [199]. Co-morbidities such as cancer, chronic infections, cardiac or peripheral vascular disease, and the risk for medical noncomplicance are carefully evaluated in this process. Depending on the regional ratio of donors to recipients and on allocation rules, waiting time for a deceased donor kidney can vary from a few months (e.g. Belgium, Austria) to many years (e.g. Germany). Thus, the option of living kidney donation should be explored.

To test for eligibility, potential donors must undergo a comprehensive health assessment including tests for blood group and human leukocyte antigen compatibility with the potential recipient, GFR measures, imaging of the kidneys and the urinary tract, cardiac testing, and other tests depending on the medical history. This is because, the donor's short and long-term well-being after donation remains a first priorityPre-emptive transplantation (kidney transplantation before even initiating dialysis) may offer several benefits to ESKD patients but its impacts remain under evaluation [200]. The half-life of a transplanted kidney is <20 years, making these patients also potential candidates for CKD treatments during their life span [201]. For example, recurrent glomerulonephritis is an unpredictable complication that can have a negative impact on graft outcome [202].

840

[H2]Conservative treatment/palliative care

Kidney replacement therapy may not be available or affordable but it may also not be advisable for medical reasons. Especially in very old ESKD patients, dialysis may neither increase life span nor improve quality of life (QOL) [203-205]: in such cases palliative (trying to control the symptoms of uremia affecting QOL [206]) and education starting at CKD G4 (aimed at explaining comorbidity management) may be appropriate. Withdrawal from dialysis is a related issue and is common in very old hemodialysis patients [207].

848848

[H1] Quality of life

CKD-related symptoms increase along CKD progresses and are key drivers of poor QOL in patients with CKD and ESRKD [208-210]. In contrast, symptoms rapidly improve upon kidney transplantation. Symptoms are most severe in dialysis patients, who frequently report fatigue, nausea, dyspnea, anorexia, pruritus, restless legs, and cramps [211]. Pain is especially common: in a survey of 205 prevalent patients on hemodialysis, approximately 25% had "severe" pain during the 24h preceding the interview, and an additional 12% had "moderate pain" [212]. Mental illness including depression and anxiety are also common [213], but are understudied among people with CKD. Unfortunately, clinical and epidemiological characteristics associated with the presence, severity, onset and remission of uremic symptoms are incompletely described; their pathophysiology is poorly understood; and few drugs have been approved by regulatory authorities for their treatment [214].

Comorbidity and complications of CKD also substantially contribute to the reduced QOL in CKD patients. In some cases (e.g. anemia), effective treatments are available. In others, treatment is technically possible but has significant limitations, and treatment itself frequently causes additional symptoms and morbidity (e.g. dialytic management of hypervolemia). Despite the best efforts of clinicians, interactions between complications and their treatments can further compromise QOL for patients (e.g. volume overload resulting from sodium bicarbonate treatment of acidosis). Management of multiple comorbid conditions is already complex in patients with normal kidney function [215]; the situation is even more challenging in people with CKD, where the pathophysiology and optimal treatment of common coexisting conditions may differ from the general population (e.g. statins for coronary disease in dialysis patients). Lack of knowledge about how to prioritize and manage comorbid conditions undoubtedly contributes to the lower QOL in CKD patients through multiple mechanisms – including drug-drug and drug-condition interactions; pill burden; and decisional conflict for patients.

Dialysis is an effective life-support treatment but has many limitations in addition to those mentioned above. Key challenges for hemodialysis that specifically compromise QOL include poor

functional status (driven in part by procedure-related immobilisation, uremia-related malnutrition, and muscle wasting), the intrusive and time-consuming nature of the treatment, and vascular access infection and dysfunction [216]. Instruction for some home-based, low intensity physicial exercise can improve physical performance and QOL in patients on hemodialysis [217]. Peritoneal dialysis also poses significant challenges for QOL including gastrointestinal distension, hernias, and chronic volume overload. Both forms of dialysis make employment difficult and both are associated with a high prevalence of infectious complications and undue pill burden. Some studies suggest that peritoneal dialysis is associated with slightly better QOL than hemodialysis [218], but it is possible that this observation is confounded by patient characteristics [219]. Home dialysis strategies are constantly improving and are becoming possible tools to improve QOL [220]. Kidney transplantation is associated with substantially better QOL than either form of dialysis [221], but even recipients with good graft function must face CKD-related symptoms as well as complications of immunosuppression and other treatments.

Recent emphasis on patient-centred research should help to improve QOL for people with CKD by increasing the likelihood that important but understudied issues such as symptom control are studied and new solutions are identified. In addition, findings from patient-centred research should help to drive uptake of patient-centred care at the bedside, especially if supported by patient-reported outcomes [222]. Such paradigm shifts should help to prioritize the management of patient-important issues such as reduced QOL.

[H1] Outlook

There are many unmet medical needs in nephrology as a specialty and improving and refining our understanding of disease mechanisms in common and rarer conditions is lacking, as are novel therapies to treat rarer and common causes of kidney disease progression and a culture of curiosity and clinical trials that advance the field [37]. Key areas are to improve the identification of CKD and to reduce CKD risk factors, to improve the understanding of causes and consequences of CKD, to

improve outcomes with current knowledge, and finally to develop and test new therapeutic strategies [37]. Here, we highlight eight promising domains expected to produce significant impact on CKD management and outcomes.

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[H2]How genetic kidney disease contributes to CKD

Genetic abnormalities were identified in 20% of CKD cases in children, adolescents, and young adults. Next generation sequencing have unveiled the extreme genetic heterogeneity of kidney disease. For example more than 40 different genes were discovered as possible causes of steroid-resistant nephrotic syndrome [142]. This requires implementation of current diagnostic strategies that go beyond th renal biopsy and open to personalized diagnosis and treatments [142]. In addition, first genetic modifiers of CKD progression such as *APOL1* or *UMOD* have been identified in older adults. CKD in adults may also relate to (genetically- or environmentally-defined) low nephron endowment or AKI episodes early in life, e.g. as early as during neonatal (intensive) care. Thus, CKD in adults, often classified by a single diagnosis, may often be the consequence of several components accumulating with time, a conclusion having important implications for the design of CKD trials, e.g. in prevalent entities such as “diabetic nephropathy”. Progress will require identifying the cause(s) of CKD and dissecting modifiable from non-modifiable drivers of CKD progression as well as specific pathophysiological mechanisms that might help to define more homogeneous patient subgroups. The identification of such subgroups is a prerequisite to conducting more targeted clinical trials, which require fewer participants and increase the possibility to identify appropriate drugs for different subtypes of patients. Patient heterogeneity is considered one of the main reasons why clinical trials in nephrology commonly fail [223]. Genetic investigations might therefore not only hold promise for individual patients, for example by facilitating the diagnosis of a monogenic disease with potential implications for individualized treatment, but might also improve classification and ultimately treatment and/or prevention in groups of patients [224]. The study of the genetic predisposition to kidney diseases has made major progress over the past decade. For the first time,

researchers have been able to carry out genome-wide screens to study complex kidney diseases, to which genetic susceptibility variants in many genes, as well as environmental factors, contribute. Genome-wide association studies (GWAS) have emerged as an important method to map risk loci for complex dis- eases by investigating the association of genetic markers across the genome with the disease of interest. We can predict that the list of genetic forms of CKD will exponentially increase together with our understanding of the genetic component of kidney function in health and disease [224].

[H2]Biomarkers for CKD management

As discussed, using serum creatinine-based diagnosis implies diagnosis as late as CKD G3, leaving a small window of opportunity for modulating CKD progression. Earlier identification CKD with biomarkers that can also predict CKD progression would help to initiate nephroprotective interventions [37]. Most attractive would be a marker of nephron number. Defining nephron number at birth would display low nephron endowment and help to dissect it from injury- or ageing-related nephron loss later in life. A marker of nephron number would detect CKD G2 and could serve as an end point parameter for clinical trials to quantify nephro-protective effects or drug toxicity. However, identifying a clinically applicable biomarker of nephron number in serum or urine has been unsuccessful so far. Biomarkers do not clearly discriminate nephron number from the compensatory increase in mass of remnant nephrons upon injury (remnant nephron hypertrophy). Imaging studies with tracers or the combination of imaging with kidney biopsy indicating the number of glomeruli and even SNGFR are promising as a proof-of-concept [85, 225].

[H2]Separating triggers of nephron loss from CKD progression

Congenital low nephron endowment, obesity, and AKI/CKD-related nephron loss imply hyperfiltration and hypertrophy of the remnant nephrons, which in turn promote secondary FSGS and further nephron loss. Interstitial fibrosis most likely represents matrix replacement of lost

nephrons, thereby stabilizing the remnant nephrons. Whether fibrosis itself contributes to nephron loss remains under debate and several antifibrotic drugs are under study to test this concept [226, 227]. Dissecting the relative contribution of nephron injury, wound healing, and compensatory hyperfiltration remains notoriously difficult in clinical practice. Finding ways to define their relative contribution and selectively target these mechanisms in a personalized manner remains a challenge for the following years.

[H2] Modifying CKD progression

Among the many ideas on how to potentially modulate CKD progression some accumulated a large fundament of experimental evidence but still await successful validation in human RCTs (e.g. protecting nephron loss by modulating kidney fibrosis) [228]. In contrast, the idea to retard CKD progression with urate-lowering therapies already showed promising results in smaller trials and the results of ongoing multicenter RCT are eagerly awaited [229]. In contrast, the nuclear factor (erythroid-derived 2)-like (NRF)-2 agonist bardoxolone or folic acid supplementation have shown nephroprotective effects in RCTs in some populations but their mechanisms-of-action are not yet fully understood [182, 230,231].

[H2]Nephrogenesis and regeneration

Given the significant hurdles preventing widespread use of renal transplantation, Current work is exploring whether the transfer of autologous stem (progenitor) cells, stromal cells or other cell types can support the regeneration of injured nephrons (FIG. 8). For this to be a viable option, a growing research field is trying to unravel the physiology and pathophysiology of the nephron's intrinsic capacity to regenerate.

Several studies have identified possible drugable targets to specifically enhance nephron regeneration with pharmacologic intervention to prevent nephron loss in AKI and CKD [232]. In particular, targeting parietal epithelial cells that can act as progenitor for podocytes, to promote

their differentiation into fully functional podocytes and/or to block their excessive proliferation and matrix production can promote remission of glomerular disorders [233-235]. In addition, enhancing tubular regeneration by promoting tubular epithelial cell proliferation can reduce the occurrence of CKD after AKI [234, 236]. Although in vivo experimental studies appear promising, no clinical trials are available yet [233-235]. Finally, numerous Inhibitors of maladaptive repair induced improved tissue structure and even function in experimental models of CKD. Several phase 1-2 clinical trials were started but up to now, but none progressed beyond phase 2 [237]. However, other new antifibrotic drugs display are currently being tested in clinical trials [234, 237,238].

Regenerative medicine is also being explored for treatment of kidney disorders. Therapeutic properties mesenchymal stroma cells (MSC), a population of well-characterized, easily obtainable cells with effective in numerous but not all experimental models of CKD [239, 240]. The underlying mechanisms of action of the MSC have been extensively described and consist essentially in immunomodulatory and paracrine effects. Similarly, numerous experimental studies reported improvement of kidney function and/or structure by using injection of human renal progenitors [232-236]. However, the translation of preclinical studies into robust, effective, and safe patient therapies remains limited [233, 234,237].

Finally, the generation of 3D organ-buds termed 'organoids' from human induced pluripotent stem cells and embryonic stem cells was achieved also for the kidney; these organoids consist of a variety of renal cell types in vitro that mimic organs in vivo [241, 242]. The organoid bears great potential in the study of human diseases in vitro, especially when combined with CRISPR/Cas9-based genome-editing [243, 244]. However, the complexity of kidney structure and function is yet far from being reproduced for the purpose of clinical use for renal replacement therapy and the question if and when this will be eventually possible is still open.

[H2]Animal models and RCT design

Innovative approaches to better link translational research to clinical trial findings will need to start with well-defined human genotypes and phenotypes to identify molecular targets, which may (or may not) subsequently be validated in animal models. Selecting such animal models for validation should be based on models that recapitulate CKD progression in humans and applying identical end points in subsequent clinical trials. This may include mice with identical pathogenic mutations as in human genetic kidney disease as being available for Alport syndrome, mouse models with a partial human immune system, or eventually experimentation in pigs or primates to close gaps between preclinical and clinical trials [245, 246].

In addition, trial design may be improved upon reconsidering disease definitions, avoiding add-on designs using drugs with redundant mechanisms-of-action, preselecting patients with drug mechanisms-related biomarkers, and of study end points that better predict CKD progression to ESKD. For example, in order to test efficacy of the C5a receptor inhibitor avacopan in ANCA vasculitis the CLEAR trial at first avoided the usual add-on standard of care approach and compared instead avacopan plus low-dose steroids versus placebo plus high dose steroids on top of either cyclophosphamide or rituximab [247]. This way it was proven that avacopan is effective in replacing high-dose glucocorticoids in treating vasculitis.

[H2]Limiting cardiovascular morbidity and mortality

Targeting the association of CKD with cardiovascular morbidity and mortality will require more functional studies in animals and humans to identify molecular targets potentially suitable for therapeutic interventions [37]. Controlling hyperlipidemia with PCSK9 inhibitors, suppressing systemic inflammation with innovative anti-inflammatory drugs, modulating the intestinal microbiota, or directly modulating vascular calcificaton and cardiac fibrosis may offer new solutions for this eminent problem in the future.

[H2]Translation of advances into daily practice

The ever growing complexity of kidney biopsy reading, lab diagnostics, and the increasing need for genetic testing will require centers of excellence with sufficient resources to meet the diagnostic demands. The same may apply to upcoming costly therapies, where patient selection is of particular importance. Educational efforts are also needed to alert patients and general physicians to the increasing number of more affordable therapeutic options for CKD patients with diabetes, such as SGLT2 inhibitors. Finally, national CKD registries and treatment guidelines advocate awareness in the public, among health care providers, and decision takers, which can generate important support for implementation of standards [37]. Global guidelines created by the KDIGO initiative have become instrumental in this process starting from a global definition of CKD stages up to defining standards for the management of CKD complications (Box 3). In addition, global initiatives on CKD launched by the International Society of Nephrology define knowledge gaps in CKD and propose how to address them in the future [37].

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Box 1. Risk factors for chronic kidney disease

- Diabetes mellitus (type 1 or 2)
- Poorly controlled arterial hypertension
- Obesity
- Monogenetic kidney disease (for example, autosomal dominant polycystic kidney disease, podocytopathies causing steroid-resistant nephrotic syndrome, Fabry's disease and Alport syndrome, complementopathies such as atypical haemolytic-uremic syndrome (aHUS)
- Prolonged exposure to nephrotoxins (e.g., chemotherapy for cancer treatment, proton pump inhibitors, non-steroidal anti-inflammatory drugs, and anti-microbial agents), contaminated herbs, agricultural chemicals, heavy metals, irradiation)
- Climate (excessive heat exposure and dehydration)
- Infections and chronic inflammation (HIV, HCV, HBV, malaria, bacterial infections urinary

tract infections, rheumatic disorders and autoimmune diseases)

- Malignancy (especially lymphocyte and plasma cell disorders such as multiple myeloma)
- Congenital renal abnormalities (CAKUT, vesico-ureteric reflux)
- Episodes of acute kidney injury

- Low nephron endowment at birth (low birth weight, fetal dysmaturity)
- Obstructive uropathy
- Systemic vasculitis
- Hyperhomocysteinemia

Box 2. Biochemical and serologic tests useful for defining causes of CKD

[H1]*Auto-immune disease*

- Fluorescent anti-nuclear antibody, anti-dsDNA antibody, anti-phospholipaseA2 receptor antibody, anti-GBM antibody, anti-neutrophil cytoplasmic antibody, anti-phospholipid antibody
- Serum hemolytic complement activity (C'H50), serum C3 and C4 levels, cryoimmunoglobulins

[H1]*Malignancy*

- Serum free light chains, serum or urinary immunofixation (multiple myeloma)
- Serum albumin, phosphorous, total proteins and albumin/globulin ratio

[H1]*Infections*

- Human Immunodeficiency Virus, hepatitis B virus, hepatitis C virus serology, CD4+ T cell counts, urine, blood cultures, anti-streptococcal antibody tests

[H1]*Monogenetic kidney disease*

- Serum or urinary enzymes, glycolipids
- Genetic testing using next generation and Sanger sequencing

Box 3. Key strategies to managing CKD complications

[H1]Renal anemia [187]

- Erythropoeiesis stimulating agents (ESAs) are only given once all correctable causes of anemia (e.g. iron deficiency and inflammatory states) have been addressed
- Adults received Iron supplementation when transferrin saturation is <30% and ferritin <500 ng/ml; children (<18 years) receive Iron supplementation when transferrin saturation is <20% and ferritin <100 ng/ml
- ESAs may be used to avoid hemoglobin <9.0 g/l with a target of max.11.5 g/dl
- Avoid blood transfusion whenever possible, especially in potential transplant recipients. Caution in giving ESAs in people at risk of stroke or who have malignancy

[H1]Arterial hypertension [188]

- Individualize blood pressure (BP) targets are based on age and co-morbidities, with special recommendations for diabetes
- Targets include normalizing body weight (BMI 20-25), NaCl intake (<5g/d), achieving regular physical exercise, limiting alcohol intake to 2 drinks/d (men), 1 drink/day (women)

[H1]Mineral and bone disorder [189, 248]

- Monitor calcium, phosphorus, parathyroid hormone, and alkaline phosphatase activityin adults beginning in CKD G3a and in children beginning in with CKD G2 ; 25(OH)D levels might also be measured and corrected by vitamin D supplementation as for the general population
- In CKD G3a-G5D lower elevated phosphate levels toward the normal range but avoid hypercalcemia by restricting the dose of calcium-based phosphate binders
- Avoid long-term exposure to aluminium in phosphate binders or dialysate
- Measure bone mass density in patients with CKD G3a-G5D with evidence of bone disease to assess fracture risk if results will impact treatmentIn adults calcitriol and vitamin D

analogues are no longer recommended for routine use unless secondary hyperparathyroidism in CKD G4-G5 is severe and progressive

- For patients with CKD G5D PTH-lowering therapy calcimimetics, calcitriol, or vitamin D analogs are recommended
- Consider patients with vascular calcifications at high risk for cardiovascular disease; avoid calcium-based phosphate binders in these patients, limit dietary phosphate intake.

[H1]Hyperlipidemia [249]

- Adults >50y with CKD should receive a statin; when eGFR <60ml/min, statin or statin/ezetimibe combination should be given
- Adults <50y with CKD and other cardiovascular risk factors should receive a statin

[H1]Metabolic acidosis

- Oral bicarbonate can be used to correct mild metabolic acidosis

[H1]Chronic hyperkalemia

- Dietary restriction, loop diuretics, potassium-binding resins such as patiromer or dose

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Figure legends

Figure 1. Kidney Disease Improving Global Outcomes (KDIGO) classification of chronic kidney disease (CKD). The 2D matrix illustrates the predictive value of different levels of albuminuria and estimated glomerular filtration rate (eGFR). The color code indicates the risk for CKD progression to end-stage kidney disease (ESKD) and overall mortality. This matrix defines different stages of CKD referred as, for example, CKD G2A2 whereby the eGFR is 60-89 ml/min/1.73m^2 albuminuria is moderately increased; such a patient would have a moderately increased risk of progressing to ESKD. This staging system for CKD G2-G4 may underestimate the extent of irreversible nephron loss [251]. That is, if total GFR relies on the single nephron GFR (SNGFR) and the number of nephrons, SNGFR has to increase to compensate for reduced (or declining) number of nephrons to maintain total GFR. However, such a compensation may not occur with physiological ageing [85]. Additionally, total GFR drops if remnant nephrons are not able to increase SNGFR. Finally, increases in serum creatinine levels (representing a GFR of ≤40%) may imply remnant nephrons of ≤30% of a "normal" nephron number. Furthermore, the prognosis facet of CKD classification has been developed by large-scale population-based epidemiological studies, which suffer from a "false positive" rate of- approximately 30-35% as in such studies repeat analysis after 3 months was often not available [43]. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1-150.

Figure 2. Global prevalence of treated end-stage kidney disease per 1 million population. The map depicts the prevalence of renal replacement therapy represented by kidney replacement therapy (kidney replacement therapy: hemodialysis, peritoneal dialysis, and kidney transplantation), for [Au:OK?ok] ESKD per 1 million population based on individual country data. Data not available indicates that data were either not known or not provided on the questionnaire for countries that

1168 received the survey. Reprinted with permission from Bello, A. K. et al. Assessment of
1169 Global Kidney Health Care Status. JAMA 317, 1864-1881 (2017
1170
1171 **Figure 3. Glomerular filtration rate (GFR) over time and impact of low birth weight on progression**
1172 **of CKD.** A. Population studies assessing estimated GFR document a decline in eGFR with age; here
1173 the data in men from Marocco are shown [43]. P values from P03-P97 represent the percentiles of the
1174 entire population with P50 representing mean values. This decline is a consequence of loss of
1175 functioning nephrons via glomerulosclerosis-related nephron atrophy and is not accompanied by a
1176 compensatory increase in SNGFR in the remaining intact nephrons, unlike what occurs when
1177 nephrons are lost by injury or surgery [42, 52, 85]. At age 70, nephron number is around 50% of that at
1178 age 25. Whether or not this implies increased SNGFR (single nephron hyperfiltration) of remnant
1179 nephrons or mirrors the declining demand for filtering metabolic waste is under debate but will
1180 strongly depend on co-morbidities such as obesity and the life time history of acute kidney injury
1181 episodes. In such cases, SNGFR should correlate with the total number of nephrons per body mass. B:
1182 Low birth weight (LBW) increases four-fold the relative risk to develop CKD by the age 17 as shown
1183 by population studies [69]. C: LBW status also significantly shortens the time span of when patients
1184 with IgA nephropathy reach end stage kidney disease [70].
1185
1186 **Figure 4. Contributing factors to nephron loss.** In addition to ageing, acute and chronic forms of
1187 kidney injuries further may contribute to nephron loss along life time. Environmental, genetic causes
1188 and systemic disease-related reasons for low nephron endowment or causes of nephron injury are
1189 shown during the different phases in life, when they are most commonly (but not exclusively)
1190 encountered. Combinations of such causes determine the individual risk for CKD throughout life. For
1191 example, congenital abnormalities of the urinary tract (CAKUT) can lead to end stage kidney disease
1192 (ESKD) early in life, or to secondary focal segmental glomerulosclerosis (FSGS)-related ESKD later in
1193 life. Nephrotoxic drugs such as antibiotics, pain killers, contrast media for imaging or chemotherapy

can also influence risk, as can infections (bacterial, parasitic, viral). Severe genetic defects that lead to FSGS, Alport syndrome, cysts and atypical hemolytic uremic syndrome typically become evident early in life, whereas moderate genetic defects (such as mutation in *UMOD*) can become evident in adulthood. Genetic variants in genes such as *APOL1* can modify the course of diseases such as lupus nephritis.

Figure 5. Injury, hyperfiltration and hypertrophy of the nephron. A | In response to nephron loss, single nephron hyperfiltration induces an increase in nephron size as a compensatory mechanism to maintain overall renal function. Accordingly, podocytes need to undergo hypertrophy to maintain the filtration barrier of the increasing dimensions of the filtration surface. However, podocyte hypertrophy is limited; beyond a certain threshold, barrier dysfunction first manifests as mild to moderate proteinuria. At later stages the increasing podocyte shear stress promotes podocyte detachment. Parietal epithelial cells (PEC) host putative podocyte progenitors but proteinuria and potentially other factors inhibit their potential to replace lost podocytes and rather promote scar formation, i.e. focal segmental glomerulosclerosis (FSGS). B | Hyperfiltration and proteinuria both imply an increased reabsorption work load for proximal tubules. Activated tubular cells secrete pro-inflammatory mediators that promote interstitial inflammation. Together with the progression from FSGS to global glomerulosclerosis the inflammatory microenvironment of the tubulointerstitium promotes tubular atrophy and interstitial fibrosis. Scar formation is associated with vascular rarefication and ischemia. The remnant nephrons have to further increase in size to meet the filtration demands, which accelerates the aforementioned mechanisms of CKD progression in a vicious circle.

Figure 6. The earlier-the-better: renal outcome depending on when starting renin-angiotensin system (RAS) blockade in Alport Syndrome. As shown, the time to renal replacement therapy was longest for those who started RAS inhibition early, at onset of microhematuria (usually at birth) or microalbuminuria (30-300 mg protein per day or per gram creatinine). Delaying until

macroproteinuria (>0.3g/day or per gram creatinine (green curve)) or CKD G3/4 has been established considerably shortens the time to renal replacement. Untreated patients (red curve) are relatives to

Reprinted with permission from Gross, O. et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. Kidney Int 81, 494-501 (2012).

Figure 7. Access for hemodialysis or peritoneal dialysis. A | Arteriovenous fistulae are created by surgical anastomosis of a peripheral artery with a larger subcutaneous vein, e.g. at the forearm. The increased flow and perfusion pressure leads to structural modifications in the draining vein allowing repetitive venous puncture for hemodialysis. Sometimes declining blood flow to the hand and fingers (steal phenomonen), compensatory increases in cardiac output or aneurysm formation cause problems and require surgical correction. B | Arteriovenous grafts may become necessary when the patient`s vascular status does not allow to build a fistula. Polytetrafluoroethylene grafts are mostly used and can be repetitively punctured for hemodialysis. Common problems are sterile inflammatory postimplantation syndromes or prosthetic graft infections causing bacterial sepsis. C | Central venous catheters become necessary when immediate initiation of renal replacement therapy is needed up to when a fistula or graft implant becomes ready for use. Such catheters may remain the last vascular access option for patients in which the vascular or cardiac status does not allow fistula or graft placement. Catheter infections or thrombotic complications remain constant concerns. Peritoneal dialysis requires placement of a transcutaneous catheter into the peritoneal cavity. This catheter allows fills, drains and refills of dialysate while the peritoneum serves as exchange membrane with the uremic blood. Fluid drains and refills with fresh dialysate are needed in regular intervals, usually 4 times a day.

Figure 8. Targeting kidney regeneration. In the future, it may be possible to target kidney regeneration and maladaptive repair to minimize the loss of injured nephrons and to protect the

remnant nephrons. Here, the most promising arenas of research include: 1. Enhancing podocyte regeneration. This aim may be achieved by drugs that promote differentiation into podocyte of parietal epithelial cell (PEC) progenitors of the Bowman's capsule and/or blocking their excessive proliferation. 2. Blocking fibrosis and/or maladaptive repair by inhibiting fibroblast expansion. 3. Enhancing tubular regeneration by blocking maladaptive repair and/or enhancing tubular cell proliferation [233-238].

Figure 9. Cell therapy and organoids as potential tools in CKD research and therapy. (A) Injection of two cell types, mesenchymal stromal cells and renal progenitors, were reported as possible tools for cell therapy of CKD, improving kidney function and structure in animal models. Numerous phase 1-2 clinical trials are ongoing. Several mechanisms were proposed to explain the beneficial effects observed, mostly based on secretion of paracrine factors and/or microvesicles. For renal progenitors also direct engraftment in the injured tissue was reported. (B) Kidney organoids were generated in vitro starting from induced pluripotent stem cells (iPSC) and embryonic stem cells (ESC) and used for testing of drug toxicity and modeling of kidney diseases, with or without manipulation using Crispr/Cas and other genome editing strategies.

1272 **Table 1. Therapeutic interventions for selected conditions associated with CKD risk**

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Disease entity	Diagnostic test	Therapeutic interventions
Genetic injury		
Polycystic kidney disease	Echography or MRI to detect cysts	Tolvaptan (vasopressin receptor 2 antagonist of benefit in selected patients)
Alport syndrome	Genetic testing for collagen mutations	ACE inhbitors to reduce filtration pressure in remnant nephrons
Fabry disease	Serum alpha-galactosidase activity	Alpha-galactosidase replacement therapy
Primary hyperoxaluria	Echography to detect nephrocalcinosis, urinary oxalate levels, genetic testing for serine—pyruvate aminotransferase , glyoxylate reductase/hydroxypyruvate reductase, and dihydrodipicolinate synthase-like	Increase fluid intake, supplementation with potassium citrate, magnesium oxide, pyridoxine , and orthophosphate, oxalate-reduced diet, liver transplantation
Cystinosis	Leukocyte cystine levels, slit lamp exam of the eyes, genetic testing for the cystinosin gene	Cysteamine substitution
Coenzyme Q10-related gene mutations causing FSGS	Genetic testing for AarF Domain Containing Kinase-4, coenzyme Q2, coenzyme Q6, and decaprenyl diphosphate synthase subunit 2	Coenzyme Q10 replacement therapy
C3 glomerulonephritis	Kidney biopsy, specific complement test, genetic testing for complement-related genes	Plasma exchange or blood transfusion, rituximab, eculizumab (depending on specific cause)
Immune injury		
Acute or subacute immune complex glomerulonephritis	Autoantibodies against nuclear autoantigens or neutrophil cytoplasmic antigens such as proteinase 3 or myeloperoxidase,	Immunosuppressive drugs, plasma exchange (in certain settings)

	C3/C4 serum levels urinary sediment, kidney biopsy	
Renal vasculitis	ANCAs, urinary sediment, kidney biopsy	Immunosuppressive drugs, plasma exchange (in certain settings)
Vascular injury		
Recent onset renal artery stenosis (fibromuscular or vasculitic)	Angiogram of the renal arteries	Surgical revascularization or catheter-based angioplasty
Metabolic injury		
Diabetic kidney disease	Blood glucose level, albuminuria, kidney biopsy	Antidiabetic drugs, SGLT2 blockade, RAS inhibitors
Chronic urate nephropathy	Tophaceous gout, serum uric acid levels, kidney biopsy	Purine-reduced diet, uricosuric drugs, xanthine oxidase inhibitors, rasburicase
Toxic injury		
Toxic nephropathies (lead, aristolochic acid, phenacetin, …)	History, specific toxin levels, kidney biopsy	Abandon toxin exposure
Multiple myeloma	Serum or urinary free light chain test, bone marrow aspirate, kidney biopsy	Myeloma-directed chemotherapy
Kidney infections		
Bacterial pyelonephritis	Urine culture	Increased fluid intake, antibiotics
Viral nephropathies	Viral testing, kidney biopsy	Antiviral therapy
Mechanical injury		
Obstructive nephropathy	Renal ultrasound	Relieve obstruction

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* **3**, 1-150 (2013).
2. Glassock, R., Delanaye, P. & El Nahas, M. An Age-Calibrated Classification of Chronic Kidney Disease. *JAMA* **314**, 559-60 (2015).
3. Levey, A.S., Inker, L.A. & Coresh, J. Chronic Kidney Disease in Older People. *JAMA* **314**, 557-8 (2015).
4. Poggio, E.D. et al. Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. *Kidney Int* **75**, 1079-87 (2009).
5. 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* **135**, 105-119 (2017).
6. Glassock, R.J. & Rule, A.D. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney Int* **82**, 270-7 (2012).
7. Hallan, S.I. et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* **308**, 2349-60 (2012).
8. Warnock, D.G., Delanaye, P. & Glassock, R.J. Risks for All-Cause Mortality: Stratified by Age, Estimated Glomerular Filtration Rate and Albuminuria. *Nephron* (2017).
9. De Broe, M.E., Gharbi, M.B., Zamd, M. & Elseviers, M. Why overestimate or underestimate chronic kidney disease when correct estimation is possible? *Nephrol Dial Transplant* **32**, ii136-ii141 (2017).
10. Denic, A., Glassock, R.J. & Rule, A.D. Structural and Functional Changes With the Aging Kidney. *Adv Chronic Kidney Dis* **23**, 19-28 (2016).
11. DALYs, G.B.D. & Collaborators, H. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1603-1658 (2016).
12. Jager, K.J. & Fraser, S.D.S. The ascending rank of chronic kidney disease in the global burden of disease study. *Nephrol Dial Transplant* **32**, ii121-ii128 (2017).
13. Mortality, G.B.D. & Causes of Death, C. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **385**, 117-71 (2015).
14. Thomas, B. et al. Global Cardiovascular and Renal Outcomes of Reduced GFR. *J Am Soc Nephrol* **28**, 2167-2179 (2017).
15. Zhang, L. et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet* **379**, 815-22 (2012).
16. Arora, P. et al. Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey. *CMAJ* **185**, E417-23 (2013).
17. White, S.L., Polkinghorne, K.R., Atkins, R.C. & Chadban, S.J. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis* **55**, 660-70 (2010).
18. Levey, A.S. & Coresh, J. Chronic kidney disease. *Lancet* **379**, 165-80 (2012).
19. Girndt, M., Trocchi, P., Scheidt-Nave, C., Markau, S. & Stang, A. The Prevalence of Renal Failure. Results from the German Health Interview and Examination Survey for Adults, 2008-2011 (DEGS1). *Dtsch Arztebl Int* **113**, 85-91 (2016).
20. Bruck, K. et al. CKD Prevalence Varies across the European General Population. *J Am Soc Nephrol* **27**, 2135-47 (2016).

21. Fraser, S.D. et al. Exploration of chronic kidney disease prevalence estimates using new measures of kidney function in the health survey for England. *PLoS One* **10**, e0118676 (2015).
22. Glassock, R.J., Warnock, D.G. & Delanaye, P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nat Rev Nephrol* **13**, 104-114 (2017).
23. Stanifer, J.W., Muiru, A., Jafar, T.H. & Patel, U.D. Chronic kidney disease in low- and middle-income countries. *Nephrol Dial Transplant* **31**, 868-74 (2016).
24. Stanifer, J.W. et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* **2**, e174-81 (2014).
25. Ene-Iordache, B. et al. Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross-sectional study. *Lancet Glob Health* **4**, e307-19 (2016).
26. Hill, N.R. et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS One* **11**, e0158765 (2016).
27. Jha, V. et al. Chronic kidney disease: global dimension and perspectives. *Lancet* **382**, 260-72 (2013).
28. Charlton, J.R., Springsteen, C.H. & Carmody, J.B. Nephron number and its determinants in early life: a primer. *Pediatr Nephrol* **29**, 2299-308 (2014).
29. Khalsa, D.D., Beydoun, H.A. & Carmody, J.B. Prevalence of chronic kidney disease risk factors among low birth weight adolescents. *Pediatr Nephrol* **31**, 1509-16 (2016).
30. Gifford, F.J., Gifford, R.M., Eddleston, M. & Dhaun, N. Endemic Nephropathy Around the World. *Kidney Int Rep* **2**, 282-292 (2017).
31. Glaser, J. et al. Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy. *Clin J Am Soc Nephrol* **11**, 1472-83 (2016).
32. Jayasumana, C. et al. Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. *Nephrol Dial Transplant* **32**, 234-241 (2017).
33. ESPN/ERA-EDTA Registry. Annual Report. *www.espn-reg.org/index.jsp (last accessed April 2017).* (2014).
34. Chesnaye, N. et al. Demographics of paediatric renal replacement therapy in Europe: a report of the ESPN/ERA-EDTA registry. *Pediatr Nephrol* **29**, 2403-10 (2014).
35. Saran, R. et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* **69**, A7-A8 (2017).
36. Harambat, J., van Stralen, K.J., Kim, J.J. & Tizard, E.J. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol* **27**, 363-73 (2012).
37. Levin, A. et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet* (2017).
38. Bello, A.K. et al. Assessment of Global Kidney Health Care Status. *JAMA* **317**, 1864-1881 (2017).
39. Liyanage, T. et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* **385**, 1975-82 (2015).
40. Bertram, J.F., Douglas-Denton, R.N., Diouf, B., Hughson, M.D. & Hoy, W.E. Human nephron number: implications for health and disease. *Pediatr Nephrol* **26**, 1529-33 (2011).
41. Brenner, B.M., Meyer, T.W. & Hostetter, T.H. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* **307**, 652-9 (1982).
42. Hostetter, T.H., Olson, J.L., Rennke, H.G., Venkatachalam, M.A. & Brenner, B.M. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* **241**, F85-93 (1981).
43. Benghanem Gharbi, M. et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD. *Kidney Int* **89**, 1363-71 (2016).

44. Ruggenenti, P., Cravedi, P. & Remuzzi, G. Mechanisms and treatment of CKD. *J Am Soc Nephrol* **23**, 1917-28 (2012).
45. Laouari, D. et al. TGF-alpha mediates genetic susceptibility to chronic kidney disease. *J Am Soc Nephrol* **22**, 327-35 (2011).
46. Helal, I., Fick-Brosnahan, G.M., Reed-Gitomer, B. & Schrier, R.W. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. *Nat Rev Nephrol* **8**, 293-300 (2012).
47. Grams, M.E. et al. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. *N Engl J Med* **374**, 411-21 (2016).
48. Mueller, T.F. & Luyckx, V.A. The natural history of residual renal function in transplant donors. *J Am Soc Nephrol* **23**, 1462-6 (2012).
49. D'Agati, V.D. et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. *Nat Rev Nephrol* **12**, 453-71 (2016).
50. Park, S. et al. Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of Gestational Hyperfiltration. *Clin J Am Soc Nephrol* (2017).
51. Tonneijck, L. et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. *J Am Soc Nephrol* **28**, 1023-1039 (2017).
52. Denic, A. et al. The Substantial Loss of Nephrons in Healthy Human Kidneys with Aging. *J Am Soc Nephrol* **28**, 313-320 (2017).
53. Hodgin, J.B. et al. Glomerular Aging and Focal Global Glomerulosclerosis: A Podometric Perspective. *J Am Soc Nephrol* **26**, 3162-78 (2015).
54. Kriz, W. & Lemley, K.V. The role of the podocyte in glomerulosclerosis. *Curr Opin Nephrol Hypertens* **8**, 489-97 (1999).
55. Kriz, W. & Lemley, K.V. A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. *J Am Soc Nephrol* **26**, 258-69 (2015).
56. Benigni, A., Gagliardini, E. & Remuzzi, G. Changes in glomerular perm-selectivity induced by angiotensin II imply podocyte dysfunction and slit diaphragm protein rearrangement. *Semin Nephrol* **24**, 131-40 (2004).
57. Rizzo, P. et al. Nature and mediators of parietal epithelial cell activation in glomerulonephritides of human and rat. *Am J Pathol* **183**, 1769-78 (2013).
58. Abbate, M. et al. Transforming growth factor-beta1 is up-regulated by podocytes in response to excess intraglomerular passage of proteins: a central pathway in progressive glomerulosclerosis. *Am J Pathol* **161**, 2179-93 (2002).
59. Abbate, M., Zoja, C. & Remuzzi, G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol* **17**, 2974-84 (2006).
60. Peired, A. et al. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. *J Am Soc Nephrol* **24**, 1756-68 (2013).
61. Smeets, B. et al. Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. *J Am Soc Nephrol* **22**, 1262-74 (2011).
62. Schnaper, H.W. The Tubulointerstitial Pathophysiology of Progressive Kidney Disease. *Adv Chronic Kidney Dis* **24**, 107-116 (2017).
63. Kaissling, B., Lehir, M. & Kriz, W. Renal epithelial injury and fibrosis. *Biochim Biophys Acta* **1832**, 931-9 (2013).
64. Brenner, B.M., Garcia, D.L. & Anderson, S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens* **1**, 335-47 (1988).
65. de Jong, F., Monuteaux, M.C., van Elburg, R.M., Gillman, M.W. & Belfort, M.B. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension* **59**, 226-34 (2012).
66. Low Birth, W. & Nephron Number Working, G. The Impact of Kidney Development on the Life Course: A Consensus Document for Action. *Nephron* **136**, 3-49 (2017).
67. Luyckx, V.A. & Brenner, B.M. Birth weight, malnutrition and kidney-associated outcomes--a global concern. *Nat Rev Nephrol* **11**, 135-49 (2015).

68. White, S.L. et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis* **54**, 248-61 (2009).
69. Hirano, D. et al. Association between low birth weight and childhood-onset chronic kidney disease in Japan: a combined analysis of a nationwide survey for paediatric chronic kidney disease and the National Vital Statistics Report. *Nephrol Dial Transplant* **31**, 1895-1900 (2016).
70. Ruggajo, P. et al. Low Birth Weight and Risk of Progression to End Stage Renal Disease in IgA Nephropathy--A Retrospective Registry-Based Cohort Study. *PLoS One* **11**, e0153819 (2016).
71. Becherucci, F., Roperto, R.M., Materassi, M. & Romagnani, P. Chronic kidney disease in children. *Clin Kidney J* **9**, 583-91 (2016).
72. Luyckx, V.A. et al. A developmental approach to the prevention of hypertension and kidney disease: a report from the Low Birth Weight and Nephron Number Working Group. *Lancet* (2017).
73. Keller, G., Zimmer, G., Mall, G., Ritz, E. & Amann, K. Nephron number in patients with primary hypertension. *N Engl J Med* **348**, 101-8 (2003).
74. Nicolaou, N., Renkema, K.Y., Bongers, E.M., Giles, R.H. & Knoers, N.V. Genetic, environmental, and epigenetic factors involved in CAKUT. *Nat Rev Nephrol* **11**, 720-31 (2015).
75. Cain, J.E., Di Giovanni, V., Smeeton, J. & Rosenblum, N.D. Genetics of renal hypoplasia: insights into the mechanisms controlling nephron endowment. *Pediatr Res* **68**, 91-8 (2010).
76. Uy, N. & Reidy, K. Developmental Genetics and Congenital Anomalies of the Kidney and Urinary Tract. *J Pediatr Genet* **5**, 51-60 (2016).
77. Vivante, A. & Hildebrandt, F. Exploring the genetic basis of early-onset chronic kidney disease. *Nat Rev Nephrol* **12**, 133-46 (2016).
78. Eckardt, K.U. et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management--A KDIGO consensus report. *Kidney Int* **88**, 676-83 (2015).
79. Kottgen, A. et al. Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* **41**, 712-7 (2009).
80. Reznichenko, A. et al. UMOD as a susceptibility gene for end-stage renal disease. *BMC Med Genet* **13**, 78 (2012).
81. Trudu, M. et al. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med* **19**, 1655-60 (2013).
82. Dummer, P.D. et al. APOL1 Kidney Disease Risk Variants: An Evolving Landscape. *Semin Nephrol* **35**, 222-36 (2015).
83. Kruzel-Davila, E. et al. APOL1-Mediated Cell Injury Involves Disruption of Conserved Trafficking Processes. *J Am Soc Nephrol* **28**, 1117-1130 (2017).
84. Beckerman, P. et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med* **23**, 429-438 (2017).
85. Denic, A. et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med* **376**, 2349-2357 (2017).
86. Lu, J.L. et al. Association of age and BMI with kidney function and mortality: a cohort study. *Lancet Diabetes Endocrinol* **3**, 704-14 (2015).
87. Kramer, H. et al. Waist Circumference, Body Mass Index, and ESRD in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis* **67**, 62-9 (2016).
88. Chang, A. et al. Lifestyle-related factors, obesity, and incident microalbuminuria: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Am J Kidney Dis* **62**, 267-75 (2013).
89. Ejerblad, E. et al. Obesity and risk for chronic renal failure. *J Am Soc Nephrol* **17**, 1695-702 (2006).
90. Foster, M.C. et al. Overweight, obesity, and the development of stage 3 CKD: the Framingham Heart Study. *Am J Kidney Dis* **52**, 39-48 (2008).
91. Vivante, A. et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. *Arch Intern Med* **172**, 1644-50 (2012).

92. Dunlop, W. Serial changes in renal haemodynamics during normal human pregnancy. *Br J Obstet Gynaecol* **88**, 1-9 (1981).
93. Moran, P., Baylis, P.H., Lindheimer, M.D. & Davison, J.M. Glomerular ultrafiltration in normal and preeclamptic pregnancy. *J Am Soc Nephrol* **14**, 648-52 (2003).
94. Anders, H.J., Davis, J.M. & Thurau, K. Nephron Protection in Diabetic Kidney Disease. *N Engl J Med* **375**, 2096-2098 (2016).
95. Vallon, V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med* **66**, 255-70 (2015).
96. van Bommel, E.J. et al. SGLT2 Inhibition in the Diabetic Kidney-From Mechanisms to Clinical Outcome. *Clin J Am Soc Nephrol* **12**, 700-710 (2017).
97. Anguiano Gomez, L., Lei, Y., Devarapu, S.K. & Anders, H.J. The diabetes pandemic suggests unmet needs for 'CKD with diabetes' in addition to 'diabetic nephropathy'. Implications for pre-clinical research and drug testing. *Nephrol Dial Transplant* **in press** (2017).
98. Wanner, C. et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* **375**, 323-34 (2016).
99. Bellomo, R., Kellum, J.A. & Ronco, C. Acute kidney injury. *Lancet* **380**, 756-66 (2012).
100. Venkatachalam, M.A., Weinberg, J.M., Kriz, W. & Bidani, A.K. Failed Tubule Recovery, AKI-CKD Transition, and Kidney Disease Progression. *J Am Soc Nephrol* **26**, 1765-76 (2015).
101. Barton, A.L., Mallard, A.S. & Parry, R.G. One Year's Observational Study of Acute Kidney Injury Incidence in Primary Care; Frequency of Follow-Up Serum Creatinine and Mortality Risk. *Nephron* **130**, 175-81 (2015).
102. Eckardt, K.U. et al. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* **382**, 158-69 (2013).
103. Lasagni, L., Lazzeri, E., Shankland, S.J., Anders, H.J. & Romagnani, P. Podocyte mitosis - a catastrophe. *Curr Mol Med* **13**, 13-23 (2013).
104. Liapis, H., Romagnani, P. & Anders, H.J. New insights into the pathology of podocyte loss: mitotic catastrophe. *Am J Pathol* **183**, 1364-74 (2013).
105. Portale, A.A. et al. Disordered FGF23 and mineral metabolism in children with CKD. *Clin J Am Soc Nephrol* **9**, 344-53 (2014).
106. Denburg, M.R. et al. Fracture Burden and Risk Factors in Childhood CKD: Results from the CKiD Cohort Study. *J Am Soc Nephrol* **27**, 543-50 (2016).
107. Flynn, J.T. et al. Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children study. *Hypertension* **52**, 631-7 (2008).
108. Foley, R.N., Parfrey, P.S. & Sarnak, M.J. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* **32**, S112-9 (1998).
109. Raschenberger, J. et al. Association of relative telomere length with cardiovascular disease in a large chronic kidney disease cohort: the GCKD study. *Atherosclerosis* **242**, 529-34 (2015).
110. Grabner, A. et al. Activation of Cardiac Fibroblast Growth Factor Receptor 4 Causes Left Ventricular Hypertrophy. *Cell Metab* **22**, 1020-32 (2015).
111. de Jager, D.J. et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* **302**, 1782-9 (2009).
112. De Cosmo, S., Menzaghi, C., Prudente, S. & Trischitta, V. Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence. *Nephrol Dial Transplant* **28**, 29-36 (2013).
113. Cozzolino, M., Ketteler, M. & Zehnder, D. The vitamin D system: a crosstalk between the heart and kidney. *Eur J Heart Fail* **12**, 1031-41 (2010).
114. Vervloet, M. & Cozzolino, M. Vascular calcification in chronic kidney disease: different bricks in the wall? *Kidney Int* **91**, 808-817 (2017).
115. Carrero, J.J. et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* **23**, 77-90 (2013).

116. Massy, Z.A., Metzinger-Le Meuth, V. & Metzinger, L. MicroRNAs Are Associated with Uremic Toxicity, Cardiovascular Calcification, and Disease. *Contrib Nephrol* **189**, 160-168 (2017).
117. Buglioni, A. & Burnett, J.C., Jr. Pathophysiology and the cardiorenal connection in heart failure. Circulating hormones: biomarkers or mediators. *Clin Chim Acta* **443**, 3-8 (2015).
118. Buchanan, C. et al. Intradialytic Cardiac Magnetic Resonance Imaging to Assess Cardiovascular Responses in a Short-Term Trial of Hemodiafiltration and Hemodialysis. *J Am Soc Nephrol* **28**, 1269-1277 (2017).
119. van der Heijden, B.J., van Dijk, P.C., Verrier-Jones, K., Jager, K.J. & Briggs, J.D. Renal replacement therapy in children: data from 12 registries in Europe. *Pediatr Nephrol* **19**, 213-21 (2004).
120. Tonshoff, B., Kiepe, D. & Ciarmatori, S. Growth hormone/insulin-like growth factor system in children with chronic renal failure. *Pediatr Nephrol* **20**, 279-89 (2005).
121. Rule, A.D. et al. For estimating creatinine clearance measuring muscle mass gives better results than those based on demographics. *Kidney Int* **75**, 1071-8 (2009).
122. Rule, A.D. & Glassock, R.J. GFR estimating equations: getting closer to the truth? *Clin J Am Soc Nephrol* **8**, 1414-20 (2013).
123. Stevens, L.A. et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* **75**, 652-60 (2009).
124. Inker, L.A. et al. Performance of glomerular filtration rate estimating equations in a community-based sample of Blacks and Whites: the multiethnic study of atherosclerosis. *Nephrol Dial Transplant* (2017).
125. Praditpornsilpa, K. et al. The need for robust validation for MDRD-based glomerular filtration rate estimation in various CKD populations. *Nephrol Dial Transplant* **26**, 2780-5 (2011).
126. Inker, L.A. et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* **367**, 20-9 (2012).
127. Pottel, H. et al. An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant* **31**, 798-806 (2016).
128. Delanaye, P. et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: How to measure glomerular filtration rate with iohexol? *Clin Kidney J* **9**, 682-99 (2016).
129. Delanaye, P. et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: Why to measure glomerular filtration rate with iohexol? *Clin Kidney J* **9**, 700-4 (2016).
130. Hommos, M.S., GLassock, R.J. & Rule, A.D. Structrual and functional changes in human kidneys with healthy aging. *J Am Soc Nephrol* (2017).
131. Matsushita, K. et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* **3**, 514-25 (2015).
132. Fotheringham, J., Campbell, M.J., Fogarty, D.G., El Nahas, M. & Ellam, T. Estimated albumin excretion rate versus urine albumin-creatinine ratio for the estimation of measured albumin excretion rate: derivation and validation of an estimated albumin excretion rate equation. *Am J Kidney Dis* **63**, 405-14 (2014).
133. Glassock, R.J. Evaluation of proteinuria redux. *Kidney Int* **90**, 938-940 (2016).
134. Azurmendi, P.J. et al. Early renal and vascular changes in ADPKD patients with low-grade albumin excretion and normal renal function. *Nephrol Dial Transplant* **24**, 2458-63 (2009).
135. Clark, W.F. et al. Dipstick proteinuria as a screening strategy to identify rapid renal decline. *J Am Soc Nephrol* **22**, 1729-36 (2011).
136. Glassock, R.J., Fervenza, F.C., Hebert, L. & Cameron, J.S. Nephrotic syndrome redux. *Nephrol Dial Transplant* **30**, 12-7 (2015).
137. Glassock, R.J. Con: kidney biopsy: an irreplaceable tool for patient management in nephrology. *Nephrol Dial Transplant* **30**, 528-31 (2015).

138. Jin, B. et al. The spectrum of biopsy-proven kidney diseases in elderly Chinese patients. *Nephrol Dial Transplant* **29**, 2251-9 (2014).
139. Xu, D.M., Chen, M., Zhou, F.D. & Zhao, M.H. Risk Factors for Severe Bleeding Complications in Percutaneous Renal Biopsy. *Am J Med Sci* **353**, 230-235 (2017).
140. Siwy, J. et al. Noninvasive diagnosis of chronic kidney diseases using urinary proteome analysis. *Nephrol Dial Transplant* (2016).
141. Li, J., An, C., Kang, L., Mitch, W.E. & Wang, Y. Recent Advances in Magnetic Resonance Imaging Assessment of Renal Fibrosis. *Adv Chronic Kidney Dis* **24**, 150-153 (2017).
142. Becherucci, F. et al. Lessons from genetics: is it time to revise the therapeutic approach to children with steroid-resistant nephrotic syndrome? *J Nephrol* **29**, 543-50 (2016).
143. Peralta, C.A. & Estrella, M.M. Preventive nephrology in the era of "I" evidence: should we screen for chronic kidney disease? *Kidney Int* **92**, 19-21 (2017).
144. Taal, M.W. Screening for chronic kidney disease: preventing harm or harming the healthy? *PLoS Med* **9**, e1001345 (2012).
145. Moyer, V.A. & Force, U.S.P.S.T. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* **157**, 567-70 (2012).
146. Fink, H.A. et al. Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* **156**, 570-81 (2012).
147. Caley, M., Chohan, P., Hooper, J. & Wright, N. The impact of NHS Health Checks on the prevalence of disease in general practices: a controlled study. *Br J Gen Pract* **64**, e516-21 (2014).
148. Imai, E. et al. Kidney disease screening program in Japan: history, outcome, and perspectives. *Clin J Am Soc Nephrol* **2**, 1360-6 (2007).
149. Khwaja, A. & Throssell, D. A critique of the UK NICE guidance for the detection and management of individuals with chronic kidney disease. *Nephron Clin Pract* **113**, c207-13 (2009).
150. Smith, J.M., Mott, S.A., Hoy, W.E. & International Federation of Kidney, F. Status of chronic kidney disease prevention programs: International Federation of Kidney Foundation Members 2005/2007. *Kidney Int* **74**, 1516-25 (2008).
151. Tonelli, M. et al. How to advocate for the inclusion of chronic kidney disease in a national noncommunicable chronic disease program. *Kidney Int* **85**, 1269-74 (2014).
152. Hoerger, T.J. et al. A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening. *Am J Kidney Dis* **55**, 463-73 (2010).
153. Perkovic, V. et al. Management of patients with diabetes and CKD: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* **90**, 1175-1183 (2016).
154. Ozyilmaz, A. et al. Screening for albuminuria with subsequent screening for hypertension and hypercholesterolaemia identifies subjects in whom treatment is warranted to prevent cardiovascular events. *Nephrol Dial Transplant* **28**, 2805-15 (2013).
155. Tanaka, F. et al. Low-grade albuminuria and incidence of cardiovascular disease and all-cause mortality in nondiabetic and normotensive individuals. *J Hypertens* **34**, 506-12; discussion 512 (2016).
156. Shardlow, A., McIntyre, N.J., Fluck, R.J., McIntyre, C.W. & Taal, M.W. Chronic Kidney Disease in Primary Care: Outcomes after Five Years in a Prospective Cohort Study. *PLoS Med* **13**, e1002128 (2016).
157. Grams, M.E. et al. Race, APOL1 Risk, and eGFR Decline in the General Population. *J Am Soc Nephrol* **27**, 2842-50 (2016).
158. Kovesdy, C.P., Furth, S.L., Zoccali, C. & World Kidney Day Steering, C. Obesity and Kidney Disease: Hidden Consequences of the Epidemic. *Can J Kidney Health Dis* **4**, 2054358117698669 (2017).

159. de Galan, B.E. et al. Lowering blood pressure reduces renal events in type 2 diabetes. *J Am Soc Nephrol* **20**, 883-92 (2009).
160. Oellgaard, J. et al. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. *Kidney Int* **91**, 982-988 (2017).
161. Perkovic, V. et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int* **83**, 517-23 (2013).
162. Gross, O. et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. *Kidney Int* **81**, 494-501 (2012).
163. Schievink, B. et al. Early renin-angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes. *Diabetes Obes Metab* **18**, 64-71 (2016).
164. Oliveira, B., Kleta, R., Bockenhauer, D. & Walsh, S.B. Genetic, pathophysiological, and clinical aspects of nephrocalcinosis. *Am J Physiol Renal Physiol* **311**, F1243-F1252 (2016).
165. Trautmann, A. et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. *Clin J Am Soc Nephrol* **10**, 592-600 (2015).
166. Noris, M. & Remuzzi, G. Glomerular Diseases Dependent on Complement Activation, Including Atypical Hemolytic Uremic Syndrome, Membranoproliferative Glomerulonephritis, and C3 Glomerulopathy: Core Curriculum 2015. *Am J Kidney Dis* **66**, 359-75 (2015).
167. Hildebrand, A.M., Huang, S.H. & Clark, W.F. Plasma exchange for kidney disease: what is the best evidence? *Adv Chronic Kidney Dis* **21**, 217-27 (2014).
168. Rauen, T. et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med* **373**, 2225-36 (2015).
169. Staplin, N. et al. Smoking and Adverse Outcomes in Patients With CKD: The Study of Heart and Renal Protection (SHARP). *Am J Kidney Dis* **68**, 371-80 (2016).
170. Cravedi, P., Ruggenenti, P. & Remuzzi, G. Intensified inhibition of renin-angiotensin system: a way to improve renal protection? *Curr Hypertens Rep* **9**, 430-6 (2007).
171. Schrier, R.W. et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* **371**, 2255-66 (2014).
172. Weir, M.R. et al. Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics. *J Hypertens* **35 Suppl 1**, S57-S63 (2017).
173. Holtkamp, F.A. et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* **80**, 282-7 (2011).
174. Ruggenenti, P. et al. Role of remission clinics in the longitudinal treatment of CKD. *J Am Soc Nephrol* **19**, 1213-24 (2008).
175. Daina, E. et al. A multidrug, antiproteinuric approach to alport syndrome: a ten-year cohort study. *Nephron* **130**, 13-20 (2015).
176. Li, K. et al. Effects of Bariatric Surgery on Renal Function in Obese Patients: A Systematic Review and Meta Analysis. *PLoS One* **11**, e0163907 (2016).
177. Guideline development, g. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant* **30 Suppl 2**, ii1-142 (2015).
178. Neal, B. et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* (2017).
179. Zinman, B. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* **373**, 2117-28 (2015).
180. Wanner, C., Amann, K. & Shoji, T. The heart and vascular system in dialysis. *Lancet* **388**, 276-84 (2016).
181. Rossignol, P. et al. Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints. *Eur Heart J* (2017).

182. Xu, X. et al. Efficacy of Folic Acid Therapy on the Progression of Chronic Kidney Disease: The Renal Substudy of the China Stroke Primary Prevention Trial. *JAMA Intern Med* **176**, 1443-1450 (2016).
183. Baigent, C. et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* **377**, 2181-92 (2011).
184. Cholesterol Treatment Trialists, C. et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol* **4**, 829-39 (2016).
185. Fellstrom, B.C. et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* **360**, 1395-407 (2009).
186. Wanner, C. et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* **353**, 238-48 (2005).
187. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. . *Kidney inter., Suppl.* **2**, 279-335 (2012).
188. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. . *Kidney inter., Suppl.* **2**, 337-414 (2012).
189. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) *Kidney Int Suppl* **7**, 1-59 (2017).
190. Sumida, K. & Kovesdy, C.P. Disease Trajectories Before ESRD: Implications for Clinical Management. *Semin Nephrol* **37**, 132-143 (2017).
191. Ricardo, A.C. et al. Influence of Nephrologist Care on Management and Outcomes in Adults with Chronic Kidney Disease. *J Gen Intern Med* **31**, 22-9 (2016).
192. Kolff, W.J. The artificial kidney. *J Mt Sinai Hosp N Y* **14**, 71-9 (1947).
193. Tordoir, J. et al. EBPG on Vascular Access. *Nephrol Dial Transplant* **22 Suppl 2**, ii88-117 (2007).
194. Ravani, P. et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol* **24**, 465-73 (2013).
195. Xue, H. et al. Hemodialysis access usage patterns in the incident dialysis year and associated catheter-related complications. *Am J Kidney Dis* **61**, 123-30 (2013).
196. Alencar de Pinho, N. et al. Vascular access conversion and patient outcome after hemodialysis initiation with a nonfunctional arteriovenous access: a prospective registry-based study. *BMC Nephrol* **18**, 74 (2017).
197. Wallace, E.L. et al. Catheter Insertion and Perioperative Practices Within the ISPD North American Research Consortium. *Perit Dial Int* **36**, 382-6 (2016).
198. Leurs, P., Machowska, A. & Lindholm, B. Timing of dialysis initiation: when to start? Which treatment? *J Ren Nutr* **25**, 238-41 (2015).
199. Abramowicz, D. et al. European Renal Best Practice Guideline on kidney donor and recipient evaluation and perioperative care. *Nephrol Dial Transplant* **30**, 1790-7 (2015).
200. Sebille, V. et al. Prospective, multicenter, controlled study of quality of life, psychological adjustment process and medical outcomes of patients receiving a preemptive kidney transplant compared to a similar population of recipients after a dialysis period of less than three years--The PreKit-QoL study protocol. *BMC Nephrol* **17**, 11 (2016).
201. Chang, P. et al. Living donor age and kidney allograft half-life: implications for living donor paired exchange programs. *Clin J Am Soc Nephrol* **7**, 835-41 (2012).
202. Allen, P.J. et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. *Kidney Int* (2017).

203. Carson, R.C., Juszczak, M., Davenport, A. & Burns, A. Is maximum conservative management as an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol* **4**, 1611-9 (2009).
204. Morton, R.L. et al. Conservative Management and End-of-Life Care in an Australian Cohort with ESRD. *Clin J Am Soc Nephrol* **11**, 2195-2203 (2016).
205. Verberne, W.R. et al. Comparative Survival among Older Adults with Advanced Kidney Disease Managed Conservatively Versus with Dialysis. *Clin J Am Soc Nephrol* **11**, 633-40 (2016).
206. Crail, S., Walker, R., Brown, M. & Renal Supportive Care working, g. Renal supportive and palliative care: position statement. *Nephrology (Carlton)* **18**, 393-400 (2013).
207. Birmele, B. et al. Death after withdrawal from dialysis: the most common cause of death in a French dialysis population. *Nephrol Dial Transplant* **19**, 686-91 (2004).
208. Cox, K.J., Parshall, M.B., Hernandez, S.H., Parvez, S.Z. & Unruh, M.L. Symptoms among patients receiving in-center hemodialysis: A qualitative study. *Hemodial Int* (2016).
209. Jesky, M.D. et al. Health-Related Quality of Life Impacts Mortality but Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. *PLoS One* **11**, e0165675 (2016).
210. Rebollo Rubio, A., Morales Asencio, J.M. & Eugenia Pons Raventos, M. Depression, anxiety and health-related quality of life amongst patients who are starting dialysis treatment. *J Ren Care* (2017).
211. Davison, S.N., Jhangri, G.S. & Johnson, J.A. Cross-sectional validity of a modified Edmonton symptom assessment system in dialysis patients: a simple assessment of symptom burden. *Kidney Int* **69**, 1621-5 (2006).
212. Davison, S.N. Pain in hemodialysis patients: prevalence, cause, severity, and management. *Am J Kidney Dis* **42**, 1239-47 (2003).
213. Pereira, B.D.S. et al. Beyond quality of life: a cross sectional study on the mental health of patients with chronic kidney disease undergoing dialysis and their caregivers. *Health Qual Life Outcomes* **15**, 74 (2017).
214. Tonelli, M. The roads less traveled? Diverging research and clinical priorities for dialysis patients and those with less severe CKD. *Am J Kidney Dis* **63**, 124-32 (2014).
215. Tinetti, M.E., Fried, T.R. & Boyd, C.M. Designing health care for the most common chronic condition--multimorbidity. *JAMA* **307**, 2493-4 (2012).
216. Cabrera, V.J., Hansson, J., Kliger, A.S. & Finkelstein, F.O. Symptom Management of the Patient with CKD: The Role of Dialysis. *Clin J Am Soc Nephrol* **12**, 687-693 (2017).
217. Manfredini, F. et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. *J Am Soc Nephrol* **28**, 1259-1268 (2017).
218. Cameron, J.I., Whiteside, C., Katz, J. & Devins, G.M. Differences in quality of life across renal replacement therapies: a meta-analytic comparison. *Am J Kidney Dis* **35**, 629-37 (2000).
219. Iyasere, O.U. et al. Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of Assisted Peritoneal Dialysis with Hemodialysis. *Clin J Am Soc Nephrol* **11**, 423-30 (2016).
220. Vanholder, R. et al. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nat Rev Nephrol* **13**, 393-409 (2017).
221. Dew, M.A. et al. Does transplantation produce quality of life benefits? A quantitative analysis of the literature. *Transplantation* **64**, 1261-73 (1997).
222. Rhee, C.M., Brunelli, S.M., Subramanian, L. & Tentori, F. Measuring patient experience in dialysis: a new paradigm of quality assessment. *J Nephrol* (2017).
223. Levin, A., Lancashire, W. & Fassett, R.G. Targets, trends, excesses, and deficiencies: refocusing clinical investigation to improve patient outcomes. *Kidney Int* **83**, 1001-9 (2013).
224. Wuttke, M. & Kottgen, A. Insights into kidney diseases from genome-wide association studies. *Nat Rev Nephrol* **12**, 549-62 (2016).

225. Beeman, S.C. et al. MRI-based glomerular morphology and pathology in whole human kidneys. *Am J Physiol Renal Physiol* **306**, F1381-90 (2014).
226. Boor, P., Ostendorf, T. & Floege, J. Renal fibrosis: novel insights into mechanisms and therapeutic targets. *Nat Rev Nephrol* **6**, 643-56 (2010).
227. Tampe, D. & Zeisberg, M. Potential approaches to reverse or repair renal fibrosis. *Nat Rev Nephrol* **10**, 226-37 (2014).
228. Voelker, J. et al. Anti-TGF-beta1 Antibody Therapy in Patients with Diabetic Nephropathy. *J Am Soc Nephrol* **28**, 953-962 (2017).
229. Goicoechea, M. et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* **65**, 543-9 (2015).
230. de Zeeuw, D. et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* **369**, 2492-503 (2013).
231. Pergola, P.E. et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med* **365**, 327-36 (2011).
232. Lazzeri, E., Romagnani, P. & Lasagni, L. Stem cell therapy for kidney disease. *Expert Opin Biol Ther* **15**, 1455-68 (2015).
233. Lasagni, L. et al. Podocyte Regeneration Driven by Renal Progenitors Determines Glomerular Disease Remission and Can Be Pharmacologically Enhanced. *Stem Cell Reports* **5**, 248-63 (2015).
234. Mazzinghi, B., Romagnani, P. & Lazzeri, E. Biologic modulation in renal regeneration. *Expert Opin Biol Ther* **16**, 1403-1415 (2016).
235. Pichaiwong, W. et al. Reversibility of structural and functional damage in a model of advanced diabetic nephropathy. *J Am Soc Nephrol* **24**, 1088-102 (2013).
236. Cianciolo Cosentino, C. et al. Histone deacetylase inhibitor enhances recovery after AKI. *J Am Soc Nephrol* **24**, 943-53 (2013).
237. Klinkhammer, B.M., Goldschmeding, R., Floege, J. & Boor, P. Treatment of Renal Fibrosis-Turning Challenges into Opportunities. *Adv Chronic Kidney Dis* **24**, 117-129 (2017).
238. Kramann, R. et al. Pharmacological GLI2 inhibition prevents myofibroblast cell-cycle progression and reduces kidney fibrosis. *J Clin Invest* **125**, 2935-51 (2015).
239. Peired, A.J., Sisti, A. & Romagnani, P. Mesenchymal Stem Cell-Based Therapy for Kidney Disease: A Review of Clinical Evidence. *Stem Cells Int* **2016**, 4798639 (2016).
240. Ninichuk, V. et al. Multipotent mesenchymal stem cells reduce interstitial fibrosis but do not delay progression of chronic kidney disease in collagen4A3-deficient mice. *Kidney Int* **70**, 121-9 (2006).
241. Xinaris, C. et al. Functional Human Podocytes Generated in Organoids from Amniotic Fluid Stem Cells. *J Am Soc Nephrol* **27**, 1400-11 (2016).
242. Takasato, M. et al. Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. *Nature* **536**, 238 (2016).
243. Takasato, M. & Little, M.H. Making a Kidney Organoid Using the Directed Differentiation of Human Pluripotent Stem Cells. *Methods Mol Biol* **1597**, 195-206 (2017).
244. Xinaris, C., Brizi, V. & Remuzzi, G. Organoid Models and Applications in Biomedical Research. *Nephron* **130**, 191-9 (2015).
245. Anders, H.J., Jayne, D.R. & Rovin, B.H. Hurdles to the introduction of new therapies for immune-mediated kidney diseases. *Nat Rev Nephrol* **12**, 205-16 (2016).
246. Holderied, A. & Anders, H.J. Animal models of kidney inflammation in translational medicine. *Drug Discovery TOday: Disease Models* **11**, 19-27 (2014).
247. Jayne, D.R. et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. *J Am Soc Nephrol* (2017).
248. Ketteler, M. et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int* **92**, 26-36 (2017).

249. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. *Kidney inter., Suppl.* **3**, 259–305 (2013).
250. Farrington, K. et al. Clinical Practice Guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR<45 mL/min/1.73 m2): a summary document from the European Renal Best Practice Group. *Nephrol Dial Transplant* **32**, 9-16 (2017).
251. Klessens, C.Q. et al. An autopsy study suggests that diabetic nephropathy is underdiagnosed. *Kidney Int* **90**, 149-56 (2016).

References to highlight

Introduction:

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* **3**, 1-150 (2013).
Latest classification of CKD now implementing also albuminuria in a 2D matrix for stratification of the risk for CKD progression and complications.

Epidemiology:

Bello, A.K. et al. Assessment of Global Kidney Health Care Status. *JAMA* **317**, 1864-1881 (2017).
Latest overview about kidney health care in all regions of the world displaying wide variation of access to nephrology specialists, quality of diagnostic workup, and preferences for kidney replacement therapy.

Benghanem Gharbi, M. et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD. *Kidney Int* **89**, 1363-71 (2016).
CKD population study performed in Marocco presenting percentiles for repeated eGFR. Such GFR percentiles of the respective local population would be extremely useful for patient care.

Pathophysiology

Laouari, D. et al. TGF-alpha mediates genetic susceptibility to chronic kidney disease. *J Am Soc Nephrol* **22**, 327-35 (2011).
First description of the TGF-alpha/EGFR axis as a driver of compensatory growth of remnant nephrons. Targeting this pathway can limit the the adaptive response turning into a maladaptive pathomechanism of CKD progression.

Peired, A. et al. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. *J Am Soc Nephrol* **24**, 1756-68 (2013).
Description of how proteinuria suppresses podocyte regeneration from local podocyte precursors inside the glomerulus.

Beckerman, P. et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med* **23**, 429-438 (2017)

Mechanistic mouse studies how APOL1 risk variants destabilize stressed podocytes and promote CKD progression.

Vallon, V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med* **66**, 255-70 (2015)
Comprehensive overview on the mechanism of action of SGLT2 inhibitors in diabetic kidney disease.

Diagnosis, screening, and prevention

Chronic Kidney Disease Prognosis, C. et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* **375**, 2073-81 (2010).
Meta-analysis providing the rationale for all-cause mortality risk prediction using eGFR and albuminuria levels as implemented in the KDIGO CKD stages.
for all-cause mortality

Fink, H.A. et al. Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* **156**, 570-81 (2012).
A critical discussion of the benefits and risks of CKD screening

Lazarus, B. et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med* **176**, 238-46 (2016).
Study raising concerns about a causal link between the common use of proton pump inhibitors and CKD.

Management

Wanner, C. et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* **375**, 323-34 (2016).
First study to prove profound nephroprotective effects of an SGLT2 inhibitor in patients with CKD and diabetes

Rauen, T. et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med* **373**, 2225-36 (2015)
If well done conservative treatment is very potent in preventing CKD progression in IgA nephropathy

Ruggenenti, P. et al. Role of remission clinics in the longitudinal treatment of CKD. *J Am Soc Nephrol* **19**, 1213-24 (2008). **If rigorously done conservative treatment can be very potent in preventing CKD progression in many forms of kidney disease**

Quality of life

Rebollo Rubio, A., Morales Asencio, J.M. & Eugenia Pons Raventos, M. Depression, anxiety and health-related quality of life amongst patients who are starting dialysis treatment. *J Ren Care* (2017)

Improving quality of life starts with its proper assessment.

Iyasere, O.U. et al. Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of Assisted Peritoneal Dialysis with Hemodialysis. *Clin J Am Soc Nephrol* **11**, 423-30 (2016).
Evaluating alternative options to hemodialysis for older ESKD patients.

Outlook

Levin, A. et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet* (2017).
Roadmap on how to close gaps in global kidney health

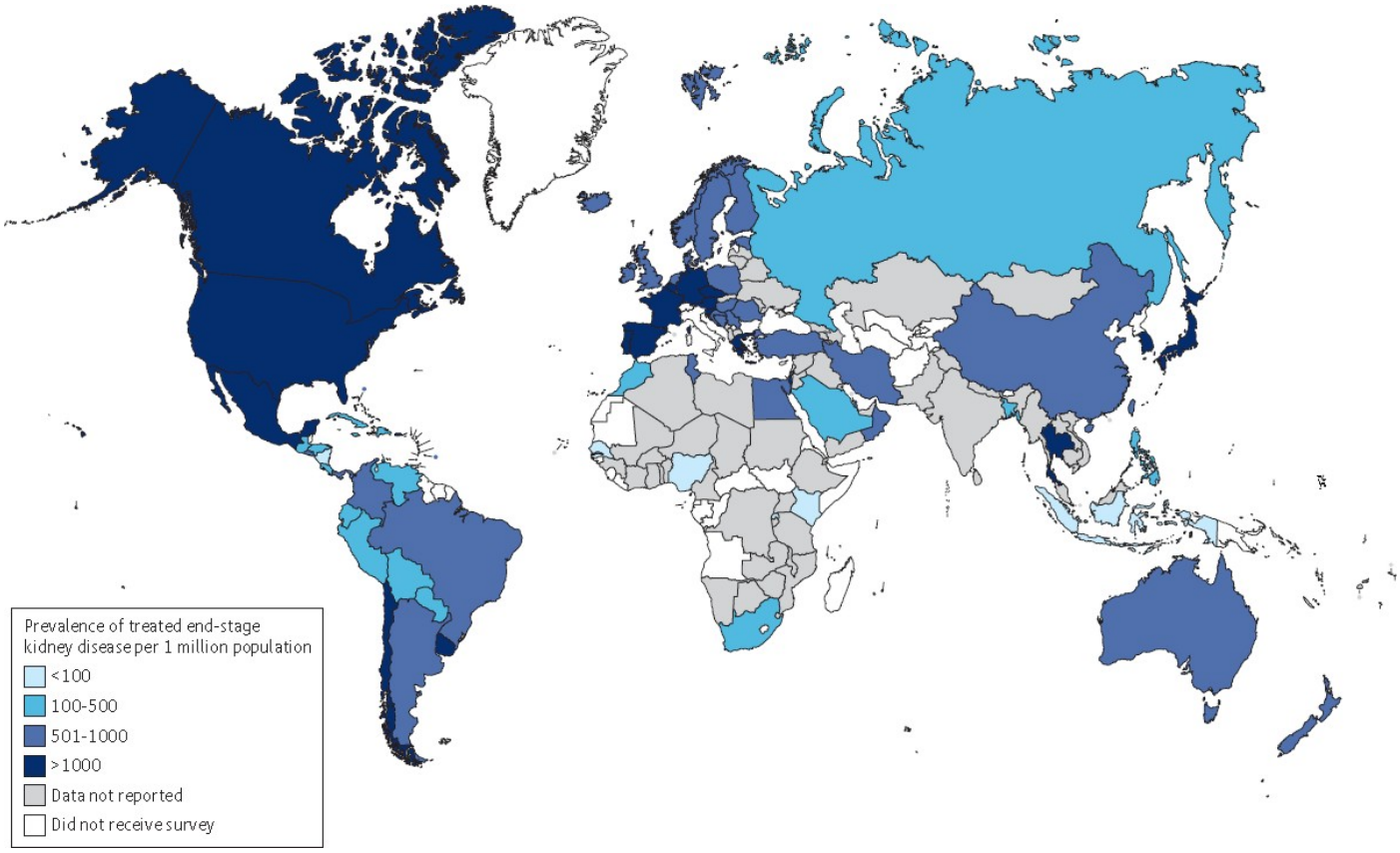
gure 1

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

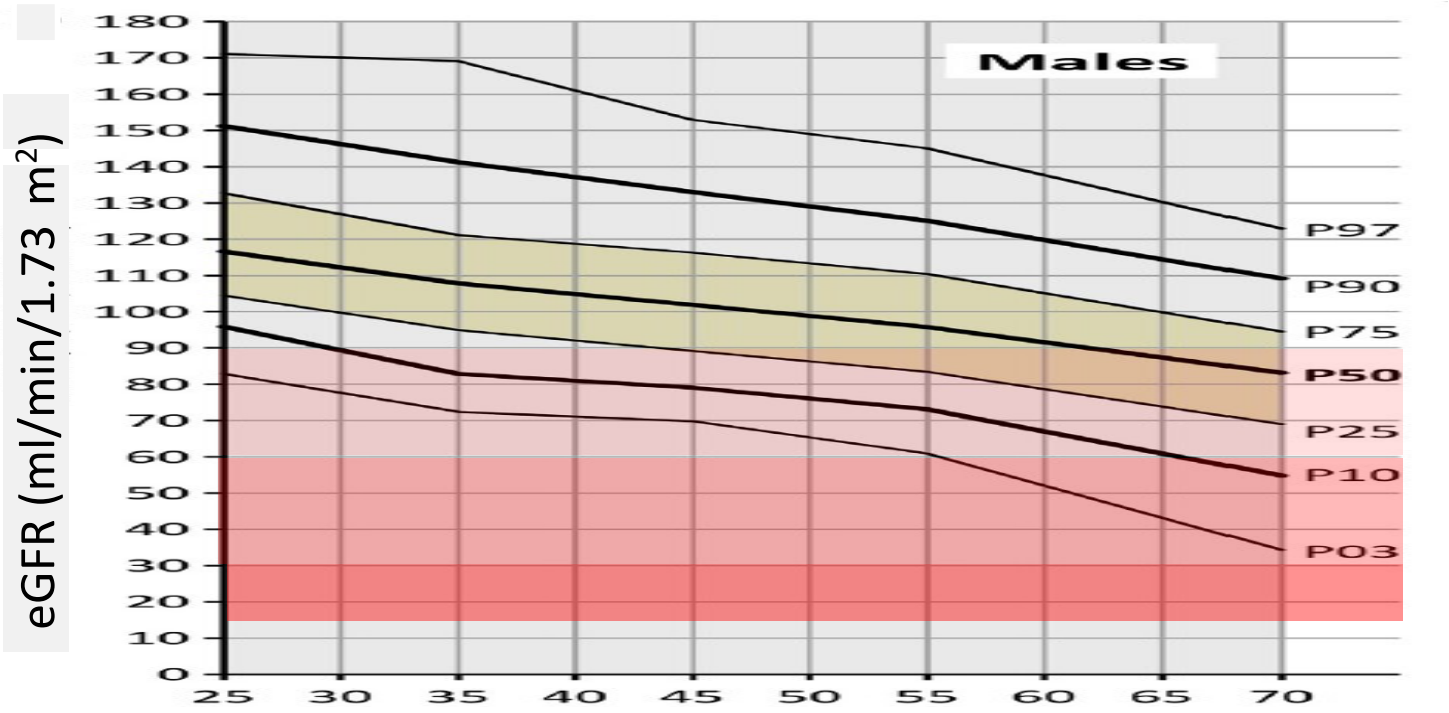
GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

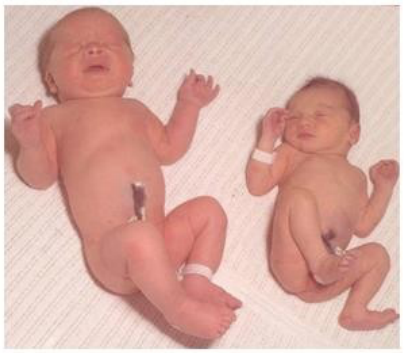
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

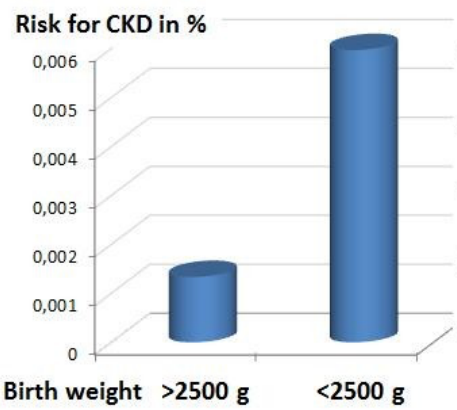
gure 2

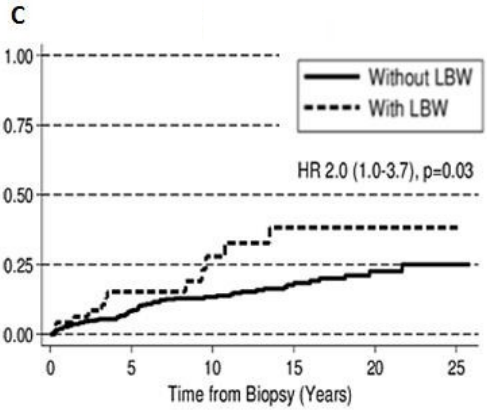

Prevalence of treated end-stage kidney disease per 1 million population
<100
100-500
501-1000
>1000
Data not reported
Did not receive survey

gure 3

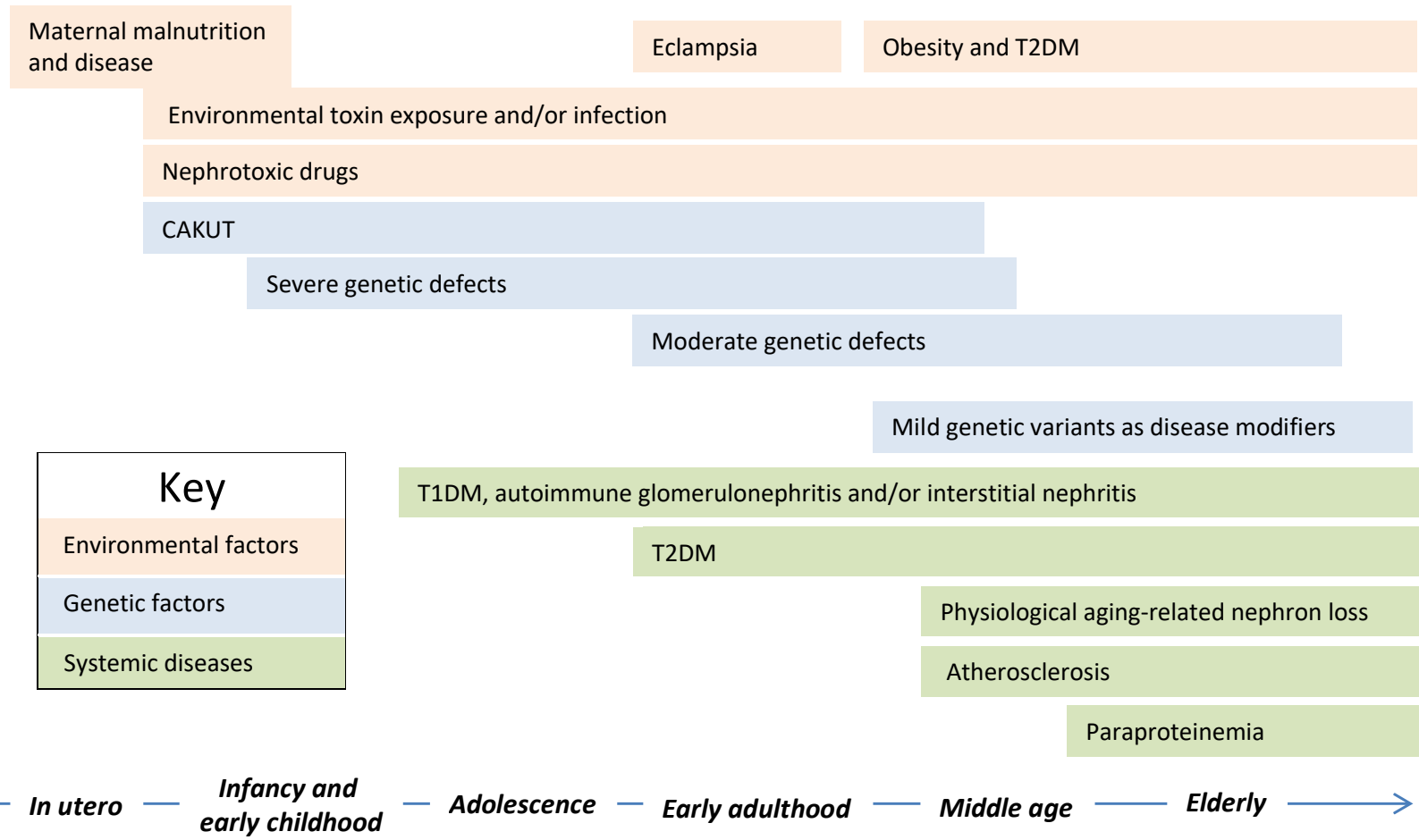

Males
eGFR (ml/min/1.73 m²)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
25
30
35
40
45
50
55
60
65
70
P97
P90
P75
P50
P25
P10
P03
Age (years)



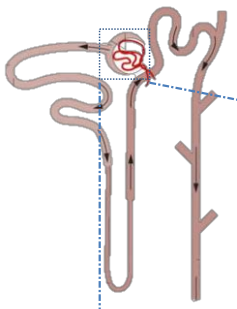

Risk for CKD in %
0,006
0,005
0,004
0,003
0,002
0,001
0
Birth weight >2500 g
<2500 g


C
1.00
0.75
0.50
0.25
0.00
Without LBW
With LBW
HR 2.0 (1.0-3.7), p=0.03
0
5
10
15
20
25
Time from Biopsy (Years)

gure 4


Maternal malnutrition and disease
Eclampsia
Obesity and T2DM
Environmental toxin exposure and/or infection
Nephrotoxic drugs
CAKUT
Severe genetic defects
Moderate genetic defects
Mild genetic variants as disease modifiers
Key
Environmental factors
Genetic factors
Systemic diseases
T1DM, autoimmune glomerulonephritis and/or interstitial nephritis
T2DM
Physiological aging-related nephron loss
Atherosclerosis
Paraproteinemia
In utero
Infancy and early childhood
Adolescence
Early adulthood
Middle age
Elderly

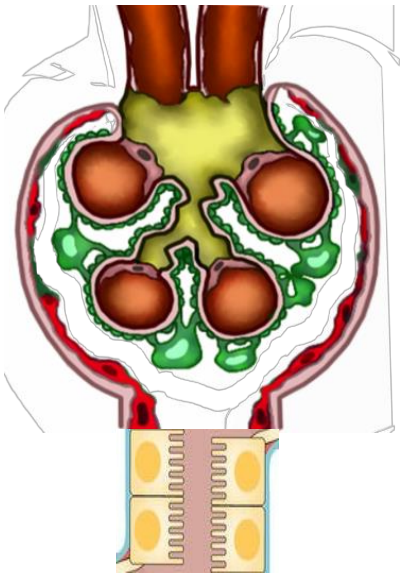
gure 5A



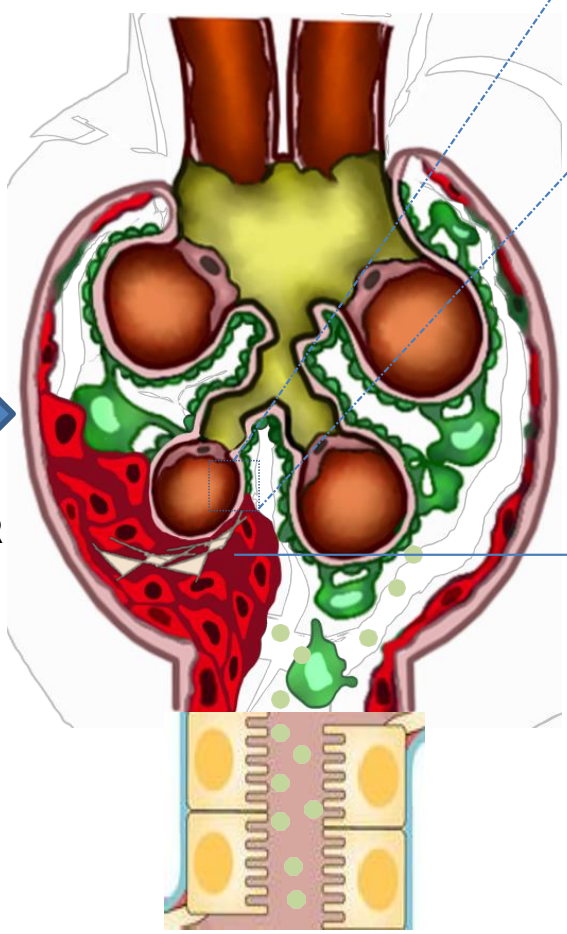
Nephron

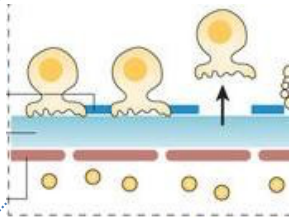
RAS activation, Na^+ retention, arterial hypertension

Glomerular hyperfiltration and hypertension



TGFα/EGFR

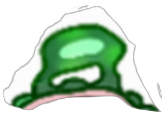




Excessive podocyte shear stress causing podocyte detachment

PEC-driven FSGS

Proteinuria

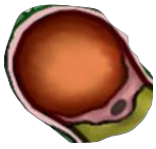


podocyte

PEC

ECM

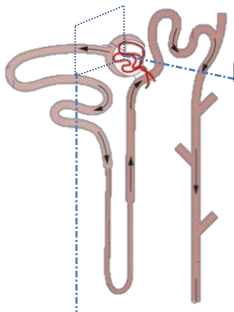
Detaching podocyte



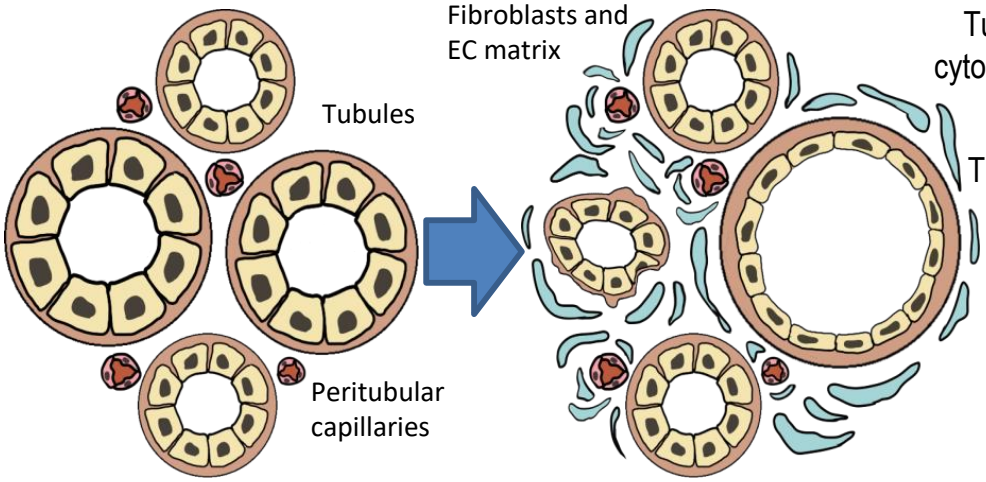
Blood vessel

proteinuria

gure 5B



Nephron



Proteinuria and misdirected filtration

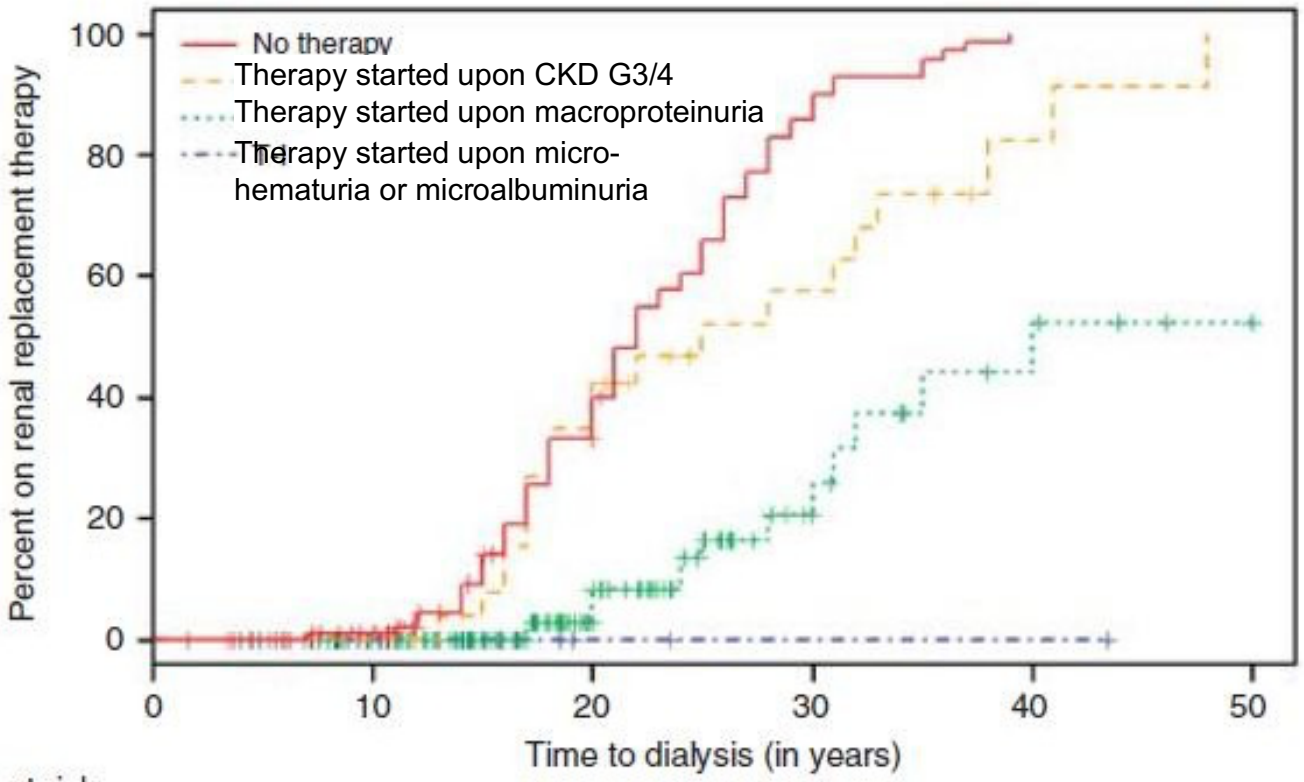
Tubular cell stress and activation to secrete cytokines and chemokines, interst. inflammation

Tubular cell loss and cell-/protein cast-related tubule obstruction causing tubule atrophy

Scar formation (interstitial fibrosis, vascular rarefication, ischemia)

Compensatory hypertrophy of tubules of the remnant nephrons

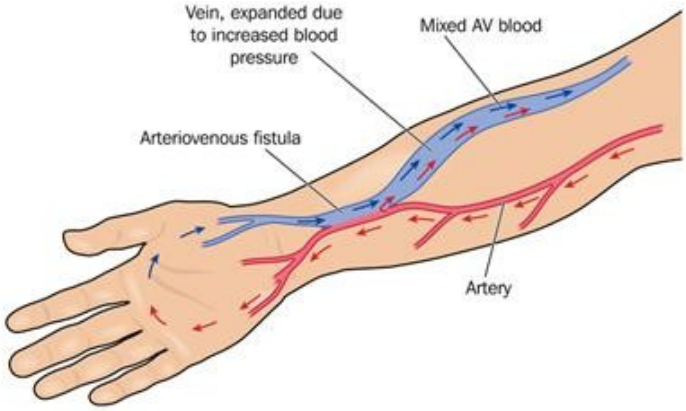
gure 6



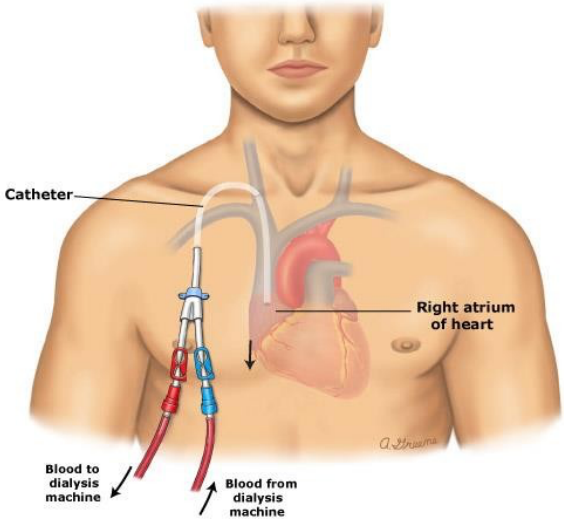
No. at risk											
No therapy	109	105	96	75	50	29	10	5	0	0	0
T-III	26	26	26	25	17	10	8	5	2	1	0
T-II	115	113	105	84	52	31	15	9	7	4	3
T-I	33	32	20	8	2	1	1	1	1	0	0

gure 7

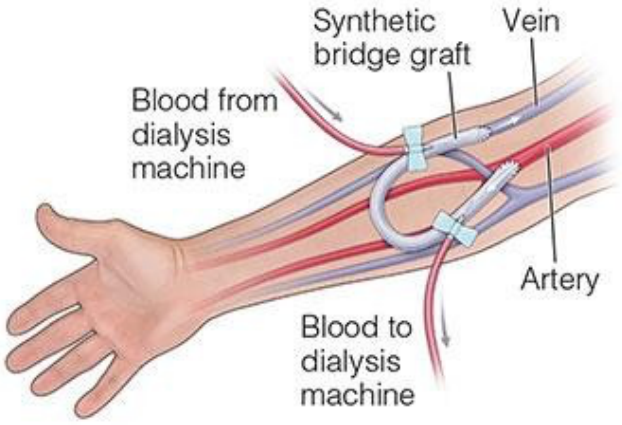
A


Vein, expanded due to increased blood pressure
Mixed AV blood
Arteriovenous fistula
Artery

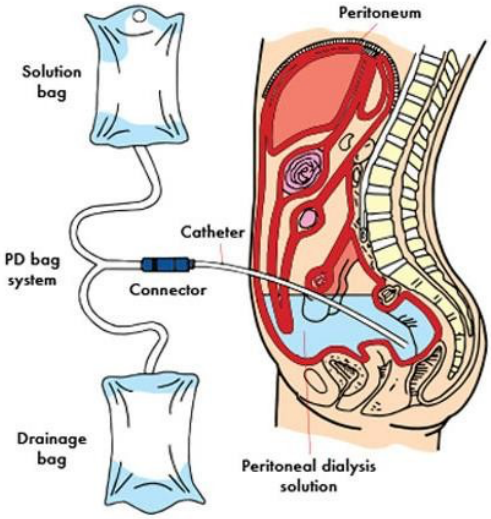
C


Catheter
Right atrium of heart
Blood to dialysis machine
Blood from dialysis machine

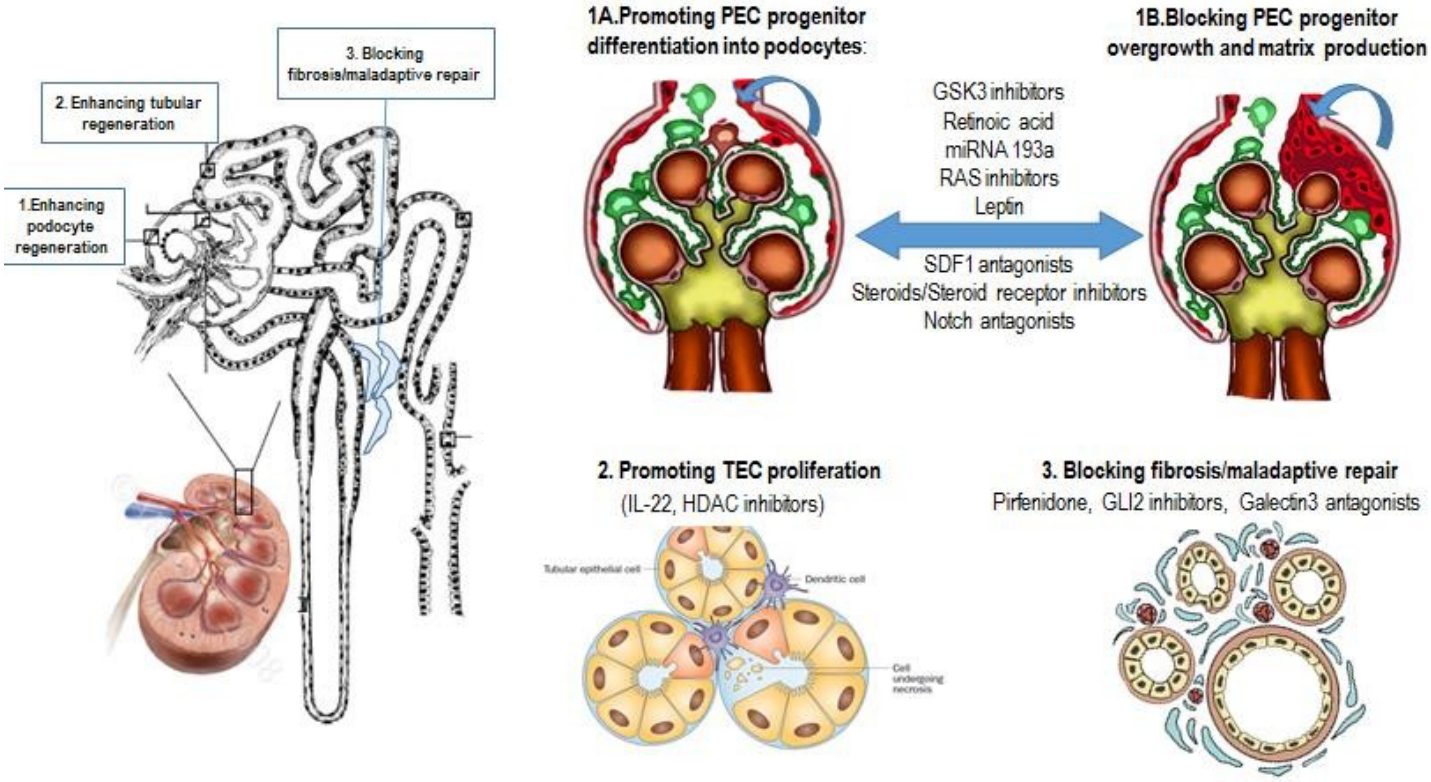
B


Synthetic bridge graft
Vein
Blood from dialysis machine
Artery
Blood to dialysis machine

D

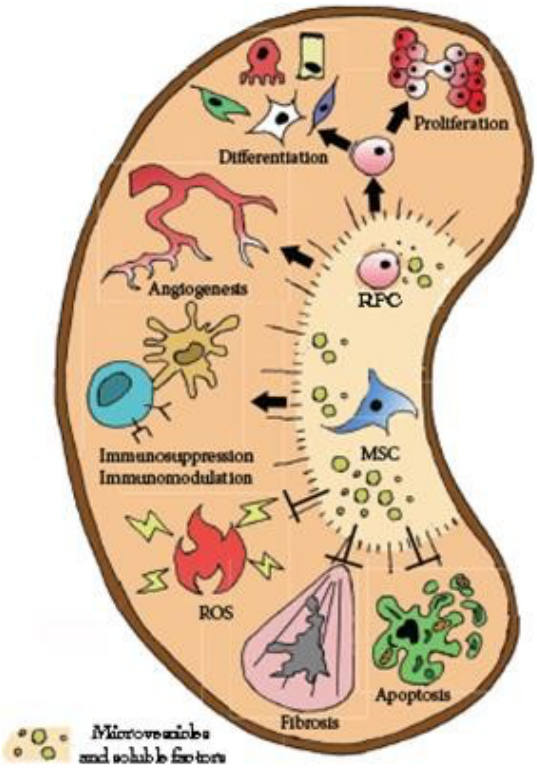

Peritoneum
Solution bag
Catheter
PD bag system
Connector
Drainage bag
Peritoneal dialysis solution

gure 8

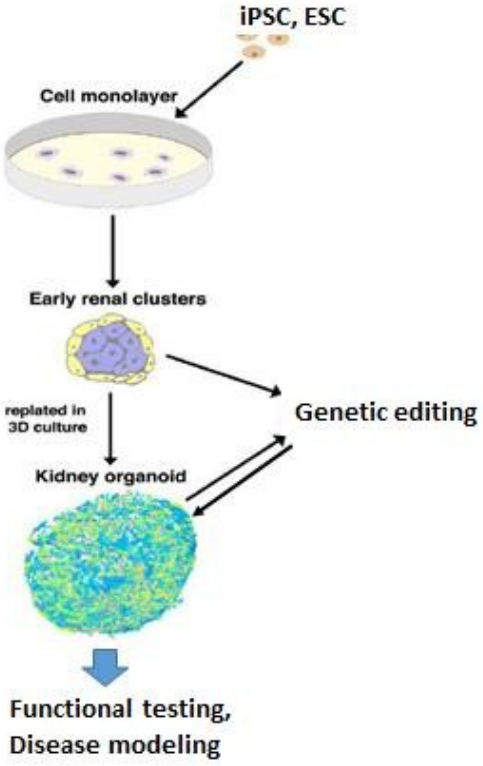

3. Blocking fibrosis/maladaptive repair
2. Enhancing tubular regeneration
1.Enhancing podocyte regeneration
1A.Promoting PEC progenitor differentiation into podocytes:
1B.Blocking PEC progenitor overgrowth and matrix production
GSK3 inhibitors
Retinoic acid
miRNA 193a
RAS inhibitors
Leptin
SDF1 antagonists
Steroids/Steroid receptor inhibitors
Notch antagonists
2. Promoting TEC proliferation
(IL-22, HDAC inhibitors)
Tubular epithelial cell
Dendritic cell
Cell undergoing necrosis
3. Blocking fibrosis/maladaptive repair
Pirfenidone, GLI2 inhibitors, Galectin3 antagonists

gure 9

A


Proliferation
Differentiation
Angiogenesis
RPC
Immunosuppression
Immunomodulation
MSC
ROS
Apoptosis
Fibrosis
Microvesicles
and soluble factors

B


iPSC, ESC
Cell monolayer
Early renal clusters
replated in
3D culture
Genetic editing
Kidney organoid
Functional testing,
Disease modeling