FLORE
Repository istituzionale dell'Università degli Studi di Firenze

Chronic kidney disease

- ?

1   **Chronic kidney disease**

2   Paola Romagnani[1], Giuseppe Remuzzi[2], Richard Glassock[3], Adeera Levin[4], Kitty J. Jager[5], Marcello

3   Tonelli[6], Ziad Massy[7], Christoph Wanner[8] and Hans-Joachim Anders[9]

4   1 Nephrology and Dialysis Unit, Meyer Children's University Hospital, Florence, Italy,
5   p.romagnani@dfc.unifi.it,
6   2 IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy, Department of Medicine,
7   Unit of Nephrology and Dialysis, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo,
8   Italy, Department of Biomedical and Clinical Science, L. Sacco, University of Milan, Milan, Italy
9   gremuzzi@marionegri.it
10   3 Department of Medicine, David Geffen School of Medicine at UCLA, 8 Bethany, Laguna Niguel,
11   92677 California, USA, rjglassock@gmail.com
12   4 Division of Nephrology, University of British Columbia, Vancouver, Canada,
13   alevin@providencehealth.bc.ca
14   5 ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam, The
15   Netherlands, k.j.jager@amc.uva.nl
16   6 Cumming School of Medicine, Division of Nephrology, University of Calgary, Calgary, Alberta,
17   Canada; Department of Community Health Sciences, University of Calgary, Calgary, Alberta,
18   Canada, cello@ucalgary.ca
19   7 Division of Nephrology, Ambroise Paré University Hospital, APHP, University of Versailles-Saint-
20   Quentin-en-Yvelines, Boulogne-Billancourt, and Inserm U1018 Team5, CESP, Villejuif, France,
21   ziad.massy@aphp.fr
22   8 Department of Medicine, Division of Nephrology, University Hospital of Würzburg, Würzburg,
23   Germany, Wanner_C@ukw.de
24   9 Medizinische Klinik and Poliklinik IV, Klinikum der LMU München – Innenstadt, Ziemssenstr. 1,
25   80336 München, Germany
26
27   **Correspondence to: H.-J.A.**
28   hjanders@med.uni-muenchen.de
29

41
42

43

44

45

46

47 **Abstract**

48 Chronic kidney disease (CKD) is defined by persistent urinary abnormalities or impaired excretory

49 renal function. While progression to end stage kidney disease (ESKD) is a concern, the majority of

50 those with CKD are at risk for accelerated cardiovascular disease and death. For those that do reach

51 ESKD the limited accessibility to kidney replacement therapy is a problem in many locations

52 worldwide.. Risk factors for CKD include low nephron number at birth and nephron loss due to

53 increasing age or acute and chronic kidney injuries. For example, the pandemic of obesity and type 2

54 diabetes largely accounts for the increasing global prevalence of CKD and there is an increasing

55 awareness of genetic causes for CKD and accelerated CKD progression. The management of CKD is

56 focused on early detection or prevention, treatment of the root cause if possible, and attention to

57 secondary processes which contribute to ongoing nephron loss, i.e. remnant nephron hyperfiltration.

58 Blood pressure control and inhibition of the renin-angiotensin system are the corner stones of

59 therapy. CKD complications such as CKD complications such as anemia, metabolic acidosis, and

60 secondary hyperparathyroidism impact cardiovascular health, as well as quality of life, and so require

61 diagnosis and therapy. Primary prevention of CKD, early diagnosis, and secondary prevention of CKD

62 progression are needed to reduce cardiovascular disease, CKD-related morbidity, and to prevent

63 ESKD, whether or not kidney replacement therapies are available.

64

65 **[H1] Introduction**

66 Chronic kidney disease (CKD) is a syndrome defined as persistent alterations in kidney

67 structure, function or both with implications for health [1]. Examples of structural abnormalities

68 include cysts, tumors, malformations or atrophy, which become evident by imaging. By contrast,

69 kidney dysfunction can become evident as hypertension, edema, growth delay in children, and

70 changes in output or quality of urine; these changes are most often recognized by increased serum

71 levels of creatinine, cystatin C or blood urea nitrogen. The most common pathological manifestation,

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

73   The Kidney Disease Improving Global Outcomes (KDIGO) initiative classifies an individual as   having

74   CKD if abnormalities of kidney structure or function persist for >3 months. KDIGO   describes a

75   classification system based on severity, into numerous stages of CKD using a two dimensional matrix

76   based on estimated or measured glomerular filtration rate (eGFR, mGFR)   and on extent of

77   albuminuria (FIG. 1) [1]. Primary care settings often do not assess albuminuria but proteinuria via dip

78   stick analysis, but dip stick +, ++, and +++ usually approximates with the three albuminuria stages.

79   GFR and albuminuria/proteinuria are used to classify CKD because GFR is a well-established marker

80   of renal excretory function and albuminuria is an indicator of renal barrier dysfunction, i.e.

81   glomerular injury. Both have found to be reliable predictors of long term CKD outcomes

82   As the kidney is formed by many independent functional and anatomical 'units', the nephrons GFR,

83   can be expressed by the equation: $GFR_{(Total)} = GFR_{(single\ nephron)} \times$ number of nephrons. This implies that

84   when the number of nephrons declines, total GFR will not change as long as single nephrons can

85   increase their individual GFR (known as single-nephron GFR (SNGFR). Vice versa, a decline in total

86   GFR implies a significant loss of nephrons with remnant nephrons probably operating at their

87   maximum possible SNGFR. That is, CKD can be thought of generally as a loss of functional nephrons

88   but usually represents loss in nephron number. Furthermore, the KDIGO stages are derived from

89   large databases of general, high risk and nephrology populations. The categories define risk of

90   progression to ESKD that is defined as G5 (GFR <15 mL/min/1.73 m[2)] and a number of other

91   outcomes including risk of cardiovascular disease (CVD), death, AKI, infections, and hospitalizations.

92   The KDIGO staging has proven to be very instrumental in decision making on patient

93   management.

94   Whether CKD should be diagnosed and staged using absolute thresholds irrespective

95   of age remains controversial [2, 3]. The mGFR in healthy adults aged 20-40 years is about 107

96   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

97   years, many otherwise healthy individuals (without significant co-morbidity) will have lost

98   50% of their nephrons and their GFR that was present at age 25 years [6]. A substantial

99   number of older healthy individuals have eGFR <60 ml/min/1.73 m^2 and no abnormal

100 albuminuria (KDIGO CKD G3a A1) meeting the KDIGO criteria for CKD albeit having only a

101 small increase in relative risk of all-cause mortality [7, 8]. The threshold of GFR that should be

102 used to detect CKD in younger persons is equally controversial [9]. The upper and lower limits for

103 mGFR in a 25 year old healthy person being considered as a living kidney donor is about 136 to 78

104 ml/min/1.73 m^2 respectively [5]; some have suggested that a threshold of <75 ml/min/1.73 m^2 would

105 be more appropriate for young adults, and values below this threshold are associated with a

106 significantly increased relative risk of all-cause mortality and ESKD [10].

107 The etiology of the impaired kidney function is important, and thus in addition to classifying the

108 severity of CKD by GFR and albumin levels, understanding the risk factors or causes of CKD is

109 essential (Box 1), and recommended by the guidelines [1]. In this Primer, we discuss the global

110 prevalence of CKD, the different diseases underlying poor nephron endowment or nephron loss, the

111 pathophysiology of CKD progression, the diagnosis, screening, and prevention of CKD, and CKD

112 management to improve outcomes and quality of life. Finally, we name several research domains

113113 potentially offering improvements for CKD management in the near future.

114114

115   [H1] Epidemiology

116   Rates of age-standardized death and disability due to most non-communicable diseases have

117 decreased over the past 20 years, but such favourable trends are not present for CKD. The Global

118 Burden of Disease study reports indicate an increase burden of CKD (with substantial worldwide

119 variation) to which diabetes mellitus seems to be the most important contributor [11-13]. CKD as a cause

120 of mortality has increases over the last 25 years from 21st to 13th', and now contributes 1.35% of the

121 global burden of disability life years lost, growing at a rate of 1% per annum [11, 13, 14]. Note that most

122 prevalence data are based on levels of GFR only, without consideration of albuminuria, based on the

123 first CKD classification system reported in 2002.

124

[H2] Prevalence

126   CKD stage G3–5 prevalence in adults varies worldwide, with values reported as 1.7% in China

127   [15], 3.1% in Canada [16], 5.8% in Australia [17] and 6.7% in the USA [18]. In Europe the range is slightly

128   narrower: from 2.3% in Germany [19], 2.4% in Finland [20], 4.0% in Spain [20] to 5.2% in England [21]. Such

129   numbers should be viewed with caution because they are often based on a single eGFR assessment

130   (that is not considering the actual definition, which includes the factor of time (present for >3 mo;

131   thus it is possible that positive "CKD cases" may overestimate the true prevalence of CKD [22]. The

132   epidemiology of CKD in low and middle-income countries (LMICs) is poorly characterized due to the

133   lack of community-based studies, inconsistent assessment of kidney function and non-standardized

134   or non-calibrated approaches[23]. Nevertheless, in South-East Asia, some Latin American countries

135   (such as Mexico) and in sub-Saharan Africa, when assessed, the prevalence of CKD appears to be

136   consistent with the estimates of 10-16% [23-25].

137

[H2] Risk factors

139   CKD is more common in people over 65 but the probability of progression to ESKD is higher in

140   younger people with CKD, albeit sometimes over long period of times [26]. Interestingly,while the

141   prevalence of CKD is higher in women than in men, men are more likely to progress to ESKD [26]. The

142   most common underlying diseases are diabetes mellitus and hypertension, particularly in in high and

143   middle income countries. In those with diabetes, CKD prevalence is estimated in 30- 40%. Whether

144   this is due to diabetes per se or due to microvascular disease is not known. However, in LMICs, CKD

145   is often due to infectious diseases and glomerulonephritis (a group of diseases that lead to

146   inflammation of the glomerulus) [27]. Current and future changes in socio-economic circumstances and

147   population age distributions will increase the absolute number of people with CKD in these countries,

148   where numbers of elderly persons are rising, and with increasing diabetes and obesity epidemic, may

149   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].

161161

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].

171171

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

176 people progress to ESKD, estimates of those with CKD can be extrapolated; conversely if CKD rates

177 are known then numbers on dialysis can reveal inequities in availability of dialysis. Data on the

178 incidence of kidney replacement therapy for ESKD can only be obtained from countries with dialysis

179 registries. Data are missing in particular from LMICs, where such registries do not exist. In 2014,

180 incidence of kidney replacement therapy varied from 49 per million population (pmp) in Bangladesh

181 to as high as 455 pmp in Taiwan [38]. The majority of patients started kidney replacement therapy on

182 dialysis, because pre-emptive transplantation as an initial modality is not freely available. Kidney

183 transplant rates differed substantially by country from 1 pmp in Bangladesh to 60 pmp in Jalisco

184 (Mexico). There was also huge variation in the prevalence of kidney replacement therapy (FIG. 2):

185 from 113 pmp in Bangladesh to 3,219 pmp in Taiwan [38].

186 In many European countries, more than half of all kidney replacement therapy patients are

187 transplant recipients [38]. This is in contrast to the situation in some Asian countries like Taiwan, Japan

188 and the Philippines where kidney transplantation is hardly performed [38]. There are multiple reasons

189 why transplantation is not available despite the availability of expensive dialysis services: cultural,

190 socioeconomic and health care infrastructure deficiencies (lack of biopsy services, lack of surgeons,

191 lack of immunology laboratories) account for many of these. Existence of available dialysis and

192 transplant services has not been systematically documented; however the Global Kidney Health Atlas

193 [[38]; full report at *www.theisn.org*] describes availability of kidney replacement therapy worldwide.

194 Note that the registry data for dialysis and transplantation described above does not reflect the true

195 need for kidney replacement therapy, which may account for the wide variability in incidence and

196 prevalence. Estimates of unmet need vary from 2 to 7 million people per year [39]. Note that

197 availability and accessibility are not the same, and even when services ae available in a country or

198 region, not all individuals may have access to them (depending on cost reimbursement, demand, and

199199 specific policies).

200200

201201

8

202

[H1]Mechanisms/pathophysiology

[H2] Nephron loss and compensation

205   In humans, nephrons are generated from the 12th-36th week of gestation with a mean

206   number of 950,000 per kidney in a range from approximately 200,000 to >2.5 million [40]. No new

207   nephrons can form upon injury and, during growth from childhood to adulthood, the available

208   nephrons increase in size to accommodate increased renal demands. However, as people age, GFR

209   declines (FIG. 3). Although nephrons can deal with transient increases in filtration load (such as upon

210   food and fluid intake) by transient increases in SNGFR ("renal reserve") [41, 42], longer or persistent

211   increases in body mass (for example, during pregnancy or obesity) promote nephron hypertrophy as

212   the compensatory mechanism. Any injury- (or kidney donation-)related nephron loss may have the

213   same effect (FIG. 4). Indeed, either severe kidney injury or combinations of injury with ageing-related

214   nephron losses — especially in individuals with poor nephron endowment and/or obesity —

215   accelerates persistent increased SNGFR and loss of remnant nephrons[43].

216   Remnant nephron hypertrophy is triggered by persistent elevations of SNGFR and filtration

217   pressure (that is, glomerular hypertension) across the glomerular filtration barrier, which implies

218   glomerular hyperfiltration. Specifically, glomerular hyperfiltration and hypertension together

219   promote the release of tumour growth factor-alpha/epithelial growth factor receptor [44, 45], leading to

220   nephron hypertrophy that reduces glomerular hypertension by increasing filtration surface [46].

221   Indeed, increased SNGFR and remnant nephron hypertrophy allows kidney donors to maintain an

222   apparently "normal" renal function, despite lacking 50% of nephrons. Obviously, kidney donation

223   does not necessarily cause CKD progression when donors are carefully selected for good nephron

224   endowment, the absence of obesity, diabetes, and ongoing nephron injury [47, 48]. However, in other

225   circumstances, hyperfiltration-driven increases in glomerular dimensions can potentially be harmful

226   [42, 46, 49-51]. Beyond a certain threshold of hypertrophy, increasing podocyte (which are key octopus-

227   shaped cells that maintain the glomerular filtration barrier of the nephron shear stress promotes

9

228   podocyte detachment, focal segmental glomerulosclerosis (FSGS, a pathological entity in which renal

229   injury results in sclerotic lesions in segments of glomeruli), global glomerulosclerosis and subsequent

230   nephron atrophy, a vicious cycle further reducing nephron number and the SNGFR of remnant

231   nephrons (FIG. 5) [44, 46,52-55].

232

233   **[H2] Impaired glomerular filtration and fibrosis**

234   Persistent podocyte hypertrophy and glomerular hyperfiltration, maintained by angiotensin II

235   production, ultimately aggravate podocyte loss and proteinuria, eventually impacting on glomerular

236   filtration Angiotensin-II, a peptide hormone that is part of the renin-angiotensin system (RAS) and

237   drives vasoconstriction and aldosterone secretion (and thus sodium retention and an increase of

238   blood pressure) directly impairs the glomerular barrier sieving function, possibly via inhibiting

239   expression of the podocyte protein nephrin, a structural component of the slit diaphragm necessary

240   for maintaining the glomerular filtration barrierindependently of its hemodynamic effects [56].

241   Angiotensin-II possibly also contributes to the dysregulated response of parietal epithelial cell

242   precursors along Bowman`s capsule, generating FSGS lesions instead of replacing lost podocytes [57].

243   This structural remodelling of the glomerular tuft barrier presents clinically as proteinuria.

244   Proteinuria not only serves as a marker for nephron damage but also predicts CKD progression [44, 58,

245   59]. Mechanistically, albuminuria also impairs the capacity of parietal epithelial cells to regenerate

246   podocytes [44], instead further promoting the formation of FSGS lesions (FIG. 5) [60, 61].

247247

248   CKD progression also involves non-specific wound healing responses including interstitial fibrosis.

249   Albuminuria and complement, and infiltrating immune cells activate proximal tubular epithelial cells

250   to induce the secretion of and pro-fibrotic mediators followed by interstitial inflammation and

251   fibrosis [62]. Interstitial fibrosis is frequently considered as an additional factor driving further nephron

252   injury, e.g. via promoting renal ischemia [62] but, as in other organs, scar formation may also be

253   essential to mechanically stabilize the remaining nephrons [63]. The increased tubular transport

254 workload of remnant nephrons also involves anaerobic metabolism, intracellular acidosis, and

255 endoplasmic reticulum stress — all promoting secondary tubular cell injury [44, 60].

256256

257 [H2]Risk factors

258 Several factors can contribute to the pathogenesis of CKD, including low birth weight, pregnancy,

259 obesity, diabetes, and ageing. Each of these scenarios contributes different factors that lead to

260 and/or exacerbate nephron loss, promoting the cycles of injury and ultimately resulting in kidney

261261 failure.

262262

263 [H3]Prematurity and low birth weight.

264 Newborns with low birth weight (owing to preterm birth or intrauterine growth restriction)

265 frequently display incomplete kidney development [64-66]. Depending on the severity of prematurity,

266 poor nephron endowment can cause either early childhood CKD or CKD later in life [64-70]. The

267 associated risk was estimated among US adolescents for every 13 individuals born at low birth

268 weight, one had reduced GFR and one had raised systolic blood pressure, and this risk increases with

269 age [29]. The risk of low birth weight infants (<2599 g) to experience CKD up to the age of 17 is fourfold

270 increased compared to infants with a birth weight of >2500 g (FIG.3B) [69]. CKD onset at puberty is

271 common in these individuals when rapid body growth exceeds the capacity of nephron number to

272 accommodate the increasing filtration load[71]. In milder cases, poor nephron endowment at birth

273 promotes the development of hypertension, CKD later in adults or a faster progression of

274 glomerulonephritis to ESKD (FIG.3C) [29, 66, 70, 72, 73]. All of these factors increase the risk of

275 cardiovascular disease.

276

277 [H3]Genetic factors.

278 Congenital abnormalities of the kidney and the urinary tract (CAKUT) are the most common

279 congenital abnormalities [74]. CAKUT present a wide spectrum of causes for kidney hypodysplasia,

11

280 imparting low nephron number and risk of CKD later in life[75, 76]. Genetic testing has revealed that

281 ~20% of early-onset CKD (defined as CKD manifesting before 25 years of age) cases can be attributed

282 to a monogenic cause [77]. Beyond CAKUT, these conditions include ciliopathies, cystic kidney diseases,

283 tubulopathies, and podocytopathies causing FSGS [75-78].

284 Until recently, monogenic causes of CKD were mostly reported in children or adolescents, but

285 genetic variants also contribute as co-factors to CKD progression in adults (FIG. 4). For example, an

286 UMOD gene variant, present on 17% of the alleles in the general population, is associated with CKD

287 [79-81]. Another example is gene variants of apolipoprotein L1 (APOL1) in African Americans, which

288 confer resistance to Trypanosoma brucei infections in sub-Saharan Africa [82]. However, these variants

289 affect endosomal trafficking and autophagic flux, which ultimately leads to podocyte loss,

290 glomerulosclerosis, nephron loss, and CKD progression [83, 84]. This may explain faster CKD progression

291 in many patients with sub-Saharan ancestry [82].

292292

293 **[H3]Obesity.**

294 A larger glomerular size on mildly obese (BMI>30 and <35) but otherwise healthy individuals suggests

295 an increased SNGFR [85]. In general, the association between obesity and poorer renal outcomes

296 persists even after adjustments for higher blood pressure and diabetes mellitus, suggesting that

297 obesity-driven glomerular hyperfiltration directly contributes to nephron loss [86, 87]. Severe obesity

298 alone or moderate obesity in combination with other factors such as genetic, low nephron number

299 or aging can lead to development of proteinuria, secondary FSGS, and progressive CKD (FIG. 4) [86, 88-91].

300300

301 **[H3]Pregnancy.**

302 The latter trimester of pregnancy involves volume expansion (that is, an increase in blood volume)

303 causing an increase of total GFR by 50% [92], implying a respective increase of SNGFR. These

304 physiological adaptations are transient and without consequences in women with normal nephron

305 number. However, in women with low nephron endowment or previous injury-related CKD (such as

306 in women with lupus nephritis), pregnancy-related glomerular hyperfiltration exacerbates remnant

307 nephron glomerular hyperfiltration and hypertrophy. In some patients, final trimester pregnancy-

308 related glomerular hyperfiltration then passes the threshold of compensation and triggers rapid CKD

309 progression presenting with proteinuria and hypertension — a condition known as eclampsia. Pre-

310 existing CKD G3A2 or higher, obesity, excessive body weight increase during pregnancy are well-

311 known risk-factors for eclampsia [93].

312312

313 [H3]Diabetes.

314 Diabetes is a well-known condition associated with massive glomerular hyperfiltration, evident from

315 increased total GFR and renomegaly [51]. Hyperglycemia promotes the sodium-glucose transporter

316 (SGLT)-2-driven reabsorption of sodium in the proximal tubule, a process that subsequently

317 inactivates tubuloglomerular feedback and activates the RAS at the *macula densa* [94, 95]. The result is

318 induction of a permanent dilation of the afferent arteriole and vasoconstriction of the efferent

319 arteriole — permanently increasing SNGFR and total GFR [96].

320 Although diabetes-driven glomerular hyperfiltration can be compensated for many years in

321 younger patients with normal nephron number, it serves as a drastic accelerator single nephron

322 hyperfiltration such as patients with low nephron endowment, injury- or ageing-related nephron

323 loss, obesity or those who are pregnant [97]. Unfortunately, this is a highly prevalent combination of

324 risk factors in older patients with type 2 diabetes, for which dual SGLT2/RAS inhibition can elicit

325 potent nephroprotective effects [98].

326326

327 [H3]Acute kidney injury.

328 Acute kidney injury (AKI) is a clinical syndrome defined by an acute deterioration of renal function

329 resulting in the accumulation of metabolic waste and toxins, subsequent uremic complications, and

330 potentially failure of other organs [99]. AKI is highly prevalent in hospitalized patients and can imply

331 irreversible losses in nephron number[100]. In Western countries AKI occurs in both outpatient and

332 inpatient settings, the latter of which is simpler to document, and has been the focus of multiple

333 papers describing the phenomenon and aiding in the understanding of the strong association

334 between AKI and CKD. The causes of non hopsital/institutuion-based AKI are diarrhea, infections,

335 dehydration, medications, while in hospital it can be attributed to these same factors and exposures

336 to nephrotoxins (dye) and is mostly observed in patients with multiple morbidities [101]. By contrast, in

337 LMICs and tropical countries, AKI occurs frequently outside the hospital setting following episodes of

338 diarrhoea, infections and obstetric complications [102]. Nephrotoxins can also cause AKI-related

339 nephron loss inside and outside hospitals; for example, neonates treated with aminoglycosides,

340 cancer patients receiving chemotherapy or communities exposed to environmental toxins such as

341 heavy metals or aristolochic acid can experience AKI episodes [30].

342342

343 **[H3]Ageing.**

344 The slope of GFR decline varies among individuals depending upon age (FIG. 3), genetic factors, blood

345 pressure, diseases implying kidney injury and body weight. Histologically, kidney ageing presents as

346 global glomerulosclerosis, the respective atrophy of entire nephrons, and subsequent interstitial

347 fibrosis [53, 85]. Whether ageing-related nephron loss is associated with hypertrophy (and glomerular

348 hyperfiltration) of remnant nephrons is not consistently reported in the literature [53, 85], but the

349 analytical difficulties on how to precisely assess nephron number, glomerular volume, and how to

350 acknowledge the different functions of juxtamedullary versus cortical nephrons can affect the

351 interpretation of such data [53, 85]. Ageing is associated with decreasing podocyte density and total

352 numbers [53]. Endomitosis-related mitotic catastrophe and podocyte detachment may contribute to

353 glomerulosclerosis[53, 103, 104].

354354

355 **[H2]Systemic effects**

356 The kidney is involved in multiple complex hormonal processes important in anemia, bone

357 integrity, in regulation of acid base and electrolyte homeostasis, as well as blood pressure control

358   through neuroendocrine and volume sensors. As nephron mass declines, patients will suffer from

359   complications associated with dysregulation of many of these systems. Anemia, vitamin D deficiency,

360   hyperparathyroidism, acidosis, hyperkalemia and hyperphosphatemia, hyperuricemia, as well as

361   hypertension and expansion of effective circulating fluid volume are all clinical manifestations of

362   these derangements. Interestingly, they do not occur in all individuals at the same point in the

363   progressive loss of kidney function, and there are some maintain excellent tubular/ excretory

364   function despite derangements in hormonal function (i.e. severe anemia, and normal electrolytes).

365   Not all of the derangements are symptomatic, and the severity of the symptoms is variable

366   between individuals. They include: disorders of fluid and electrolytes, mineral and bone disorder,

367   anemia, hypertension, dyslipidemia, endocrine abnormalities, in children growth impairment,

368   decreased clearance of renally excreted substances from the body (eg, hyperuricemia), metabolic

369   acidosis. Related symptoms may be fatigue, anorexia, weight loss, pruritis, nausea, vomiting,

370   muscle cramping, edema, shortness of breath, to name a few. None are specific for CKD.

371371

372   [H3] Fluid and electrolyte abnormalities.

373   **Sodium and water balance** — Sodium and intravascular volume balance are usually maintained via

374   homeostatic mechanisms until the GFR falls below 10 to 15 mL/min per 1.73 m^2. However, the

375   patient with mild to moderate CKD, despite being in relative volume balance, is less able to respond

376   to rapid infusions of sodium and is, therefore, prone to fluid overload. In some cases, especially with

377   an acute water load, hyponatremia and hypertension may occur as a consequence of fluid retention.

378   Some patients, such as those with nephronophthisis and some with obstructive uropathy, have an

379   impaired ability to concentrate urine, and have symptoms of polyuria. These children are at risk for

380   hypovolemia, as they will continue to have large urine losses even when they are volume depleted.

381   **Hyperkalemia** — In children with CKD, hyperkalemia develops due to reduced GFR causing

382   inadequate potassium excretion. Also, potassium excretion is dependent upon an exchange with

383   sodium at the distal tubule. A low GFR decreases delivery of sodium to this site where there is

384 reduction in the exchange rate with potassium into the urinary lumen. Other contributory factors for

385 hyperkalemia include: high dietary potassium intake, catabolic conditions with increased tissue

386 breakdown, metabolic acidosis, secondary type IV renal tubular acidosis (RTA) in some patients with

387 obstructive uropathy, decreased renin production by the juxtaglomerular apparatus, primary or

388 secondary hypoaldosteronism related to RAS inhibitor-related impaired cellular uptake of potassium

389

390 **[H3]Metabolic acidosis**.

391 Metabolic acidosis is observed in patients with advanced CKD and is related to the fall in total

392 ammonium excretion that occurs when the GFR decreases to below 40 to 50 mL/min per 1.73

393 m^2 (GFR category G3). In addition, there is a reduction in both titratable acid excretion (primarily as

394 phosphate) and bicarbonate reabsorption. As the patient approaches ESKD, the serum bicarbonate

395 concentration tends to stabilize between 12 and 20 mEq/L. A level <10 mEq/L is unusual, as buffering

396 of the retained hydrogen ions by various body buffers prevents a progressive fall in the bicarbonate

397397 concentration. In children with CKD, metabolic acidosis has a negative impact on growth.

398398

399 **[H3] Anemia.**

400 The anemia of CKD is due primarily to reduced renal erythropoietin production. The anemia of CKD is

401 principally normocytic and normochromic. By comparison, the finding of microcytosis may reflect

402 iron deficiency or aluminum excess, while macrocytosis may be associated with vitamin B12 or folate

403 deficiency. If left untreated, the anemia of CKD is associated with fatigue, weakness, decreased

404404 attentiveness, increased somnolence, and poor exercise tolerance.

405405

406 **[H3]Mineral bone disease.**

407 Chronic kidney disease-mineral and bone disorder (CKD-MBD) presents as a broad clinical spectrum

408 encompassing abnormalities in mineral metabolism, bone structure, and extraskeletal calcifications

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

410   calcidiol and/or calcitriol levels, and an elevated serum parathyroid hormone (PTH) and fibroblast

411   growth factor 23 (FGF-23) level [105]. Patients with more advanced CKD-MBD have bone pain, difficulty

412   in walking, and/or skeletal deformities and a higher risk of fracture [106].

413413

414   [H3]Hypertension.

415   Hypertension can be present in the earliest stages of CKD, and its prevalence increases with

416   progressive declines in GFR. Hypertension is high in children with CKD, ranging from 54 to 70 percent

417   of patients [107]. Hypertension is due to activation of the RAS and volume expansion. In some cases,

418   hypertension arises from corticosteroids or calcineurin inhibitors such as cyclosporine or tacrolimus

419419 used to treat the underlying kidney disease.

420420

421   [H3]Dyslipidemia.

422   Abnormal lipid metabolism is common in patients with CKD and is one of the primary factors that

423423 increase the risk for CVD.

424424

425   [H3]Hyperuricemia.

426   Elevated uric acid levels may develop in patients with CKD due to decreased urinary excretion. Serum

427   uric acid greater than 7.5 mg/dL is an independent risk factor for accelerated progression of CKD and

428428 should be treated to have a better outcome.

429429

430   [H3]Cardiovascular disease.

431   CVD is the leading cause of death in patients with CKD worldwide [14]. The increased incidence of CVD

432   is due to the high prevalence of CVD risk factors, such as hypertension, dyslipidemia, hyperuricemia,

433   abnormal glucose metabolism obesity. Young adults (25 to 34 years) with CKD have at least a 100-

434   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-

436 related cardiovascular alterations resemble all aspects of an accelerated ageing process associated

437 with a shortening of relative telomere length [109]. The vasculature can be affected by both,

438 atherosclerosis and arteriosclerosis, with lipid-rich plaques but also abundant media calcification. The

439 burden of atherosclerotic CVD increases in the early stages of CKD, and the burden of non-

440 atherosclerotic CVD increases in the more advanced stages of CKD. The „two" diseases involve

441 different factors that cause distinct changes in the risk factor profile and contribute differently to

442 outcomes during the course of CKD. Adaptive changes of the heart include left ventricular

443 hypertrophy (LVH) but also dilatation with subsequent both, systolic and diastolic dysfunction. There

444 are two different patterns of LVH: concentric LVH, which occurs in the presence of hypertension, and

445 eccentric LVH, which is associated with volume overload and anemia. Early and sustained induction

446 of fibroblast growth factor-23 was recently discovered as a driver of LVH in CKD [110].

447 The absolute risk of cardiovascular events in individuals with pre-dialysis CKD is similar to

448 that of patients with established coronary artery disease in the general population [111], and the

449 increase in risk multifactorial: a higher prevalence of insulin resistance [112], high blood pressure,

450 vascular calcification [113, 114], inflammation and protein-energy wasting [115]. ESKD is associated with a

451 range of metabolic abnormalities, the so-called milieu of uremic toxicity [116], activation of the neuro-

452 hormonal axis [117], vitamin D receptors [113], that may all contribute to accelerated ageing of the

453 vasculature and damage to the heart. Hemodialysis itself may have a direct negative effect on the

454 heart, so-called myocardial stunning [118]. As a consequence the cardiac and vascular mortality are

455 several times higher in patients with low GFR or on dialysis than in the general population. Thus, the

456 risk of CVD in patients who require dialysis depends largely on their cardiovascular health at dialysis

457 initiation. In patients with healthy arteries, the pre-dialysis management strategy should be

458 continued to prevent new cardiovascular lesions. Consequently, risk factors for CVD should be

459459 managed intensively in the pre-dialysis period, during transition, and at dialysis initiation.

460460

461 **[H3]Endocrine dysfunction.**

462 In patients with CKD, the following endocrine systems become dysfunctional as kidney function

463 progressively deteriorates. Each of these is discussed in greater detail separately. There are

464 abnormalities in gonadal hormones in both male and female patients, which can results in reduced

465 fertility and sexual problems. In children, these abnormalities result in delayed puberty in two-thirds

466 of adolescents with ESKD [119]. End-organ resistance to GH due to increased levels of insulin growth

467 factor binding proteins appears to play a major role in growth impairment in children with CKD [120].

468 Abnormalities in thyroid function can also be observed.

469 **[H3]Neurological signs.**

470 Uremia is associated with cognitive alterations ijn adults and lower performance in all neurocognitive

471 domains development in children. The neurologic findings can range from seizures and severe

472 intellectual disability to subtle deficits.

473 **[H3]Sleep and fatigue.**

474 Daytime sleepiness and fatigue are common and increase with decreasing kidney function. Sleep

475 disorders (restless leg syndrome/paroxysmal leg movements, sleep-disordered breathing, excessive

476 daytime sleepiness, and insomnia) are also common

477 **[H3]Uremia.**

478 The onset of ESKD (ie, GFR category G5) results in a constellation of signs and symptoms

479 referred to as uremia. Manifestations of the uremic state include anorexia, nausea, vomiting, growth

480 retardation, peripheral neuropathy, and central nervous system abnormalities ranging from loss of

481 concentration and lethargy to seizures, coma, and death. Patients who are uremic also have an

482 increased tendency to bleed secondary to abnormal platelet adhesion and aggregation properties.

483 Pericardial disease (pericarditis and pericardial effusion) is an indication to institute dialysis. The

484484 initiation of RRT should be considered

485485

486486

487   **[H1] Diagnosis, screening and prevention**

488   The clinical presentation of CKD depends upon the underlying disorder and the severity of renal

489   impairment. Patients with early stages of CKD G1-2 are usually asymptomatic. From CKD G3-5

490   patients may experience weakness related to anemia and polyuria. Only in late stages and in

491   untreated patients symptoms may include anorexia, vomiting, weakness, and fatigue, which are

492492   referred to as symptoms of uremia.

493493

494   **[H2]Detection and diagnosis**

495   CKD can be detected during a periodic health assessment in an asymptomatic person or during

496   evaluation of individuals at risk for CKD (Box 1); as a consequence of the incidental finding of

497   abnormal laboratory values in connection with an acute or chronic illness; during an investigation of

498   symptoms and/or signs relating to the kidneys or urinary tract (such as haematuria); or during

499   discovery of abnormal laboratory values in a population-based screening program. Importantly, the

500   two biochemical parameters (GFR and proteinuria) used in the aforementioned KDIGO matrix[1] define

501   and classify a "generic" form of CKD, and adding an etiological diagnosis is both highly desirable and

502   recommended by KDIGO (The **C**ause/**G**FR/**A**lbuminuria [CGA] classifications system), whenever

503   possible, such that the underlying conditions can be treated first to halt progression of CKD.

504   Progression is defined according to changes in eGFR by KDIGO[1]. Several tests can be performed to

505   confirm a CKD diagnosis and identify its cause. It must be stressed that a diagnosis of CKD, according

506   to the KDIGO construct, requires persistence or progression of the defining abnormality for at least 3

507507   months. A single value of GFR or albuminuria is insufficient and if used for diagnosis of CKD will lead

508508

509   **[H3] Measuring and estimating GFR.**

510   First, the assessment begins with measurement of serum creatinine concentration (under steady-

511   state conditions) and applying formulas for estimated GFR (eGFR – creatinine, like CKD-EPI eGFR-

512 creatinine). It must be recognized that the results of these creatinine based tests can be influenced

513 by changes in muscle bulk (atrophy or hypertrophy), dietary intake of cooked red meat (strict vegan

514 diet) and alterations in tubular secretion of creatinine from exposure to drugs (e.g. trimethoprim-

515 sulfamethoxazole) [121, 122]. Alternative approaches using serum cystatin_C concentrations have also

516 been proposed. While not influenced by muscled bulk and diet, the cystatin C -based formulas for

517 eGFR can be affected by inflammation, obesity, thyroid disease, diabetes, and steroid administration

518 [123]. Second, some eGFR formulashave not been extensively validated in older subjects and may not

519 apply to Asians or Africans [124, 125]. Third, the requirements for inclusion of demographic variables of

520 age and gender, to correct for differences in creatinine generation, may also create unwanted

521 complications in determining prognostic implications of a calculated GFR . Newer eGFR formulas such

522 as FAS (full age spectrum) or CKD-EPI using serum creatinine, cystatin C or a combination or Cystatin

523 C or a combination of both have improved accuracy to predict mGFR [126, 127]. Although cumbersome

524 and expensive, mGFR assessments using urinary clearance methodology can sometimes be needed,

525 but applying methods of plasma clearance of Iohexol or of radiolabelled Iothalamate could avoid

526 some of these issues. In well-defined circumstances, such as stratifying long term risks of uni-

527 nephrectomy for potential living kidney donors, such studies can be useful [128, 129]. As mentioned in

528 the introduction, caution should be exercised in using a fixed and arbitrary threshold of

529 <60ml/min/1.73m2 of GFR alone (in the absence of abnormal proteinuria or imaging) for the

530 diagnosis of CKD in older or elderly adults. A GFR of 45-59ml/min/1.73m2 is fairly common in

531 otherwise healthy seniors, depending on their age, due to the normal physiologic loss of nephrons

532 and GFR with organ senescence [130].

533533

534 [H3]Measuring proteinuria.

535 Abnormal rates of urinary excretion of albumin or total protein are essential for detection of

536 CKD when GFR is normal and contribute to the assessment of prognosis [131]. Proteinuria (or

537 albuminuria) can be determined in multiple ways, including simple "dip stick" qualitative methods,

538 point-of-care urinary albumin concentration tests, random un-timed urine samples for calculation of

539 urine protein (or albumin) to creatinine ratios (UPCR or UACR in mg/mg or mg/mmol), or timed 24

540 hour urine collections and measuring absolute protein or albumin excretion [132, 133]. Each of these has

541 advantages and pitfalls. But it is important to recognise that not all patients with CKD have abnormal

542 urinary protein excretion. For example, early in the course of Autosomal Dominant Polycystic Kidney

543 Disease the urinary protein exertion is normal only slightly increased [134].

544 Urinary protein or albumin excretion is more variable than serum creatinine levels, and can

545 be influenced by posture, activity, fever or drugs so multiple specimens must be collected to enhance

546 reliability. UPCR and UACR methods can be influenced by the prevailing urinary creatinine excretion

547 rate; i.e. low creatinine excretion (from sarcopenia) can increase UPCR or UACR values even at

548 normal absolute protein or albumin excretion rates. Hence, adjusting for the effect of urinary

549 creatinine excretion can enhance the accuracy of UPCR and UACR measurements [132, 133].

550 In the KDIGO schema, UACR values are divided into three categories [1], namely, normal or

551 low, which is <30 mg/g creatinine (<3.0 mg/mmol, formerly "normo-albuminuria"); moderately

552 increased, which is ≥30-299 mg/g creatinine (>3.0-29 mg/mmol, formerly "micro-albuminuria"); and

553 severely increased, which is ≥300 mg/g creatinine (30 mg/mmol, formerly "macro-albuminuria").

554 Even with a normal eGFR, CKD can be diagnosed with persistent UACR of >30 mg/g creatinine. Each

555 incremental increase in UACR is associated with an increased risk of mortality and ESKD, so sustained

556 albuminuria (or proteinuria) is a powerful prognostic marker.

557 The corresponding "dipstick" (urinalysis test strip) values (and protein concentration in

558 mg/dL) are negative (<10 mg/dL) to trace (10-15 mg/dL) for normal, 1+ (30 mg/dL) for moderate and

559 2+ (>100 mg/dL) or greater for severe proteinuria. Persistent proteinuria of >1+ is a good predictor of

560 a tendency for CKD progression, i.e. GFR decline of > 5 ml/min/1.73 m^2/year or 7 times the normal

561 rate of loss with ageing [135]. Thus, albuminuria or proteinuria allow early detection of CKD (see

562 Screening below), but several forms of progressive CKD can present with normal or only slightly

563 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 assessment 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

590 care of CKD is personalized based diagnostic and prognostic characteristics. Unfortunately, many

591 patients with CKD are only recognized in the later stage of the disease (Categories G3B-G5) where

592 CKD complications such anemia, metabolic acidosis, mineral-bone disease provide additional

593593 diagnostic clues.

594594

595 In addition, both detection and diagnosis of CKD, also rely on renal imaging (ultrasonography, CT and

596 MRI), careful examination of the urinary sediment, and specialized biochemical and serologic tests

597 suitable to detect specific disorders causing CKD (Box 2). Imaging tests are particularly valuable as

598 they provide information on kidney size, contours, location, and density as well as anatomy of the

599 urinary drainage system (pelvis, ureters and bladder). Specific lesions, such as cysts, dilation of

600 ureters or pelvis, calcification, masses, scars an provide valuable clues to the cause of CKD or even

601 generate a specific diagnosis (such as autosomal dominant polycystic kidney disease or obstructive

602 uropathy) [141]. Then urine sediment examination is important for the detection and quantification of

603 haematuria, leukocyturia and casts.

604 Genetic testing is also emerging as an important tool for diagnosing CKD, particularly in children or

605 young adults. Autosomal dominant polycystic kidney disease, podocytopathies causing steroid-

606 resistant nephrotic syndrome, Fabry's disease, Alport syndrome, are other well-known entities

607 requiring a genetic diagnosis. Using next-generation sequencing displays an unexpected genetic

608 heterogeneity and alterations in numerous different genes in a significant proportion of not only

609 familial or syndromic patients but also in sporadic cases of CKD. These observations imply the need

610 for updating the current management in terms of diagnostic algorithms and therapeutic choices [77,

611 142].

612

613 **[H2]Screening**

614 In the context of CKD, screening can take two forms: population screening, for example, using

615 "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].

642 Indeed, abnormal proteinuria (even only slightly above the upper limit of normal) identifies people at

643 greater risk for ESKD and/or cardiovascular morbidity and mortality [155]. As mentioned before,

644 population screening for CKD using eGFR tends to substantially over-diagnose CKD in older subjects

645 with no or minimal proteinuria. Opportunistic testing for CKD has much merit, especially if the

646 subjects have other risk factors such as diabetes, hypertension, or a family history of CKD. In such

647 patients an eGFR should be assessed along with an estimate of albuminuria or total protein excretion

648 ("dipstick"), UACR or UPCR- adjusted for creatinine excretion rate). It also must be appreciated that

649 older subjects with CKD G3 (as defined by KDIGO, see above) detected in screening programs or

650 otherwise in primary care practices tend to have a rather benign prognosis, at least over the short

651 term of 5 years or less. Shardlow et al found a very low rate of ESKD (0.2%) and stable or remission

652 of CKD was found in 53% of such subjects (average age 73 years at entry) after 5 years of follow-up

653653 [156].

654   Finally, there are a few special circumstances where testing of apparently healthy individuals

655 for CKD may be indicated. For example, first degree relatives of a patient with autosomal-dominant

656 polycystic kidney disease (ADPKD) are eligible for screening with renal ultrasound or MRI regardless

657 of results of eGFR or proteinuria. Siblings of patients with Fabry's disease, Alport syndrome, or thin

658 basement membrane nephropathy might also benefit from genetic analysis as well. African-

659 Americans with hypertension or HIV infection may receive more informed prognosis by assessment

660 of *APOL1* risk alleles, but population-based screening for *APOL1* risk alleles is not yet justifiable [157]

661661

662 [H2]Prevention

663 From a societal perspective, prevention of CKD is preferable to after- the-fact treatment of kidney

664 disease at its end-stage by dialysis or transplantation. Both primary prevention (occurring before CKD

665 is established) and secondary prevention (initiated to slow the rate of CKD progression or to affect

666 the associated co-morbidities or complications; see below, Management) should be considered.

667   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.

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,

720   NSAIDs, certain antibiotics or other endemic or occupational toxins. Hypovolemic states as well as

721   urinary outflow obstruction should be avoided. Additionally, not every asymptomatic leukocyturia

722   implies bacterial infection and antibiotic treatment should be limited to the presence of dysuria,

723   bacteriuria, and leukocyturia. Smoking cessation is essential minimize CVD [169].

724

725   [H2] Normalizing single nephron hyperfiltration

726   Rigorous RAS inhibition with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has the

727   capacity to substantially reduce SNGFR and glomerular filtration pressure, which leads to a decline in

728   not only proteinuria but also total GFR — and, hence, moderately increases serum creatinine levels

729   [170]. At first, this serum creatinine increase is worrisome to patients (and physicians) and requires

730   clarification that reducing hyperfiltration in remnant nephrons is the central strategy to retard CKD

731   progression in patients with proteinuria. In contrast, ACEi or ARBs do not retard the progression of

732   non-proteinuric forms of CKD such as ADPKD but still may have benefits on the associated

733   cardiovascular complications [171]. ACEi or ARBs should be titrated to the maximal possible dose, while

734   hyperkalemia can be corrected using loop diuretics or potassium-binding resins [172]. A moderate

735   increase in serum creatinine levels indicates a decline in SNGFR, which is a powerful predictor of the

736   intended nephroprotective effect [173]. Numerous RCTs have documented the class effect of RAS

737   inhibitors to retard or even halt CKD progression [44]. Reducing dietary salt and drugs that support

738   control of blood pressure and hyperlipidemia, often referred to as "remission clinic protocol", may

739   further reduce proteinuria and retard CKD progression [174, 175]. Such interventions are affordable and

740   are of importance where kidney replacement therapy is not available or affordable.

741   Avoiding or correcting obesity can also reduce filtration load and glomerular hypertension;

742   hence, a normal BMI is a treatment target to retard CKD progression [176]. Any immunosuppression-

743   related benefit of using steroids in CKD may be counterbalanced by steroid-related obesity that

744   drives glomerular hyperfiltration and secondary FSGS, which could explain why steroid treatment

745   falls short in retarding progression of IgA nephropathy-related CKD [168]. Finally, concomitant diabetes

31

746 has important implications for CKD management [177]. Hyperglycemia maximizes glomerular

747 hyperfiltration via SGLT2-driven vasodilation of the afferent arteriole of the remnant nephrons,

748 which cannot be controlled by RAS inhibitors [94]. Recently, SGLT2 inhibitors have been shown to

749 reverse this process and elicit profound additive nephroprotective effects on CKD progression [98, 178].

750 Their capacity to also reduce CVD (in patients with type 2 diabetes) [178, 179] provides a strong rationale

751 for dual RAS/SGLT2 blockade in patients with diabetes and CKD.

752

753 **[H2]Controlling CKD complications**

754 CKD is associated with a number of secondary complications that require management (Box 3), the

755 most relevant of which in terms of overall mortality is CVD [14]. Cardiac and vascular alterations also

756 arise from endocrine failure (e.g. lack of erythropoietin, vitamin D, parathyroid hormone), which

757 causes anemia and secondary hyperparathyroidism [180]. Myocardial fibrosis is the final consequence

758 of the multiple underlying causes.

759   Large randomized controlled trials in patients on hemodialysis have tested a number of

760 different interventions intended to reduce cardiovascular events such as dialysis dose and flux,

761 erythropoietin-stimulating agents, statins, RAS blockade, folic acid, cinacalcet or vitamin D

762 derivatives but have largely been unsuccessful [181-183]. For example, statins may prevent

763 cardiovascular events in patients on dialysis, but the magnitude of any relative reduction in risk is

764 substantially smaller as compared to what can be achieved in CKD 2-4 [183-186]. For example, reduction

765 of LDL cholesterol with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic

766 events more efficiently in patients with CKD G2-4 than with CKD G5 or 5D [183]. Hence, early

767 intervention with standard-of-care is essential in patients with CKD 2-4. In parallel, similar concepts

768 for cardiovascular protection are administered for progression of diabetic and non-diabetic kidney

769 disease. For these patients, guideline-directed approaches to achieve target blood pressure through

770 administration of RAS blockers, salt restriction and anemia prevention is the mainstay of therapy [187,

771   [188]. Guidance is also available for the correction of acidosis and mineral and bone metabolism

772   disorders (Box 3) [189].

773773

774   [H2]Preparing for kidney replacement therapy

775   ESKD typically requires renal replacement therapy, although conservative treatment is a potential

776   alternative option, especially in older adults with limited life span. Counseling on the options (kidney

777   transplant, hemodialysis, peritoneal dialysis or no dialysis) should be coordinated by the nephrologist

778   and involve a multidisciplinary team including the general practitioner. Early counseling is essential

779   because informed patients are better prepared to face kidney failure. Indeed, late referral, i.e. at the

780   time of ESKD, is associated with worse health status at the time of kidney replacement therapy

781   initiation, higher mortality after starting dialysis, and decreased access to transplant [190]. However,

782   one of the biggest challenges nephrologists face is to predict kidney disease progression, which does

783   not follow a steady linear decline. This unpredictability often becomes a barrier to timely shared

784   decision making between patients and physicians and could lead to adverse patient outcomes [190],

785   and may offset the relationship between the early pre-dialysis nephrology care for adults with late

786   stage of CKD and improved outcomes [191]. KDIGO suggested that dialysis be initiated when one or

787   more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-

788   base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a

789   progressive deterioration in nutritional status refractory to dietary intervention; or cognitive-

790   impairment [1]. This often but not invariably occurs in the GFR range between 5 and 10

791   ml/min/1.73m^2. Moreover, living donor preemptive renal transplantation in adults should be

792   considered when the GFR is <20 ml/min/1.73m^2, and there is evidence of progressive and irreversible

793   CKD over the preceding 6-12 months [1].

794794

795   [H3]Hemodialysis.

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

797   hemodialys using an artificial kidney able to clear blood from uremic toxins [192]. Since then numerous

798   technical innovations have optimized the procedure that meanwhile has become available (but not

799   everywhere affordable) all over the world [38]. Preparing patients for hemodialysis involves referral for

800   vascular access placement. The types of access include arteriovenous fistulae, arteriovenous grafts

801   and central venous catheters (which are for short-term use) (FIG. 7A-C); arteriovenous access is the

802   preferred option for hemodialysis, although there is no consensus about the optimal timing for

803   creation, especially for arteriovenous fistulae [193]. To protect the blood vessels for permanent vascular

804   access, attention should be taken to avoid venous puncture or intravenous catheter placement

805   proximal to the wrist, which implies that venous puncture at the back of the hand still being possible.

806   Arteriovenous access (either fistulae or grafts) is associated with better outcomes than central

807   venous catheters [194] [195]. Patients with a central venous catheter have poorer survival than those who

808   subsequently convert to functional arteriovenous access [196]. Thus, a functional arteriovenous access

809809   is preferable for all patients in which the vascular status allows to install a fistula.

810810

811   **[H3]Peritoneal dialysis.**

812   Peritoneal dialysis is another way to eliminate uremic toxins from the blood using the

813   peritoneal membrane as an exchange interface. For this a transcutaneous catheter is implanted into

814   the peritoneal cavity that allows repetitive daily drainage and refills of dialysate fluid. After some

815   hours of reaching equilibrium between uremic blood and fresh dialysate each dwell is expected to

816   drain excess fluid, metabolic waste products including uremic toxins (FIG. 7D). There are published

817   guidelines regarding insertion and perioperative management of peritoneal dialysis catheters. A

818   peritoneal dialysis catheter may be ready for use after 2 to 3 weeks. However, there is marked

819   variability in peritoneal dialysis catheter insertion techniques (open surgery, blind via trocar or blind

820   via Seldinger technique) and perioperative management [197]. Interestingly, patients starting on

821   peritoneal dialysis show better initial outcome and preservation of residual renal function, especially

822   in the first 2 years as compared to patients on hemodialysis [198].

824 **[H3]Kidney transplantation.**

825 When available, suitability for kidney transplantation should be evaluated according to age and co-

826 morbidities, but it may take months to complete [199]. Co-morbidities such as cancer, chronic

827 infections, cardiac or peripheral vascular disease, and the risk for medical noncomplicance are

828 carefully evaluated in this process. Depending on the regional ratio of donors to recipients and on

829 allocation rules, waiting time for a deceased donor kidney can vary from a few months (e.g. Belgium,

830 Austria) to many years (e.g. Germany). Thus, the option of living kidney donation should be explored.

831 To test for eligibility, potential donors must undergo a comprehensive health assessment

832 including tests for blood group and human leukocyte antigen compatibility with the potential

833 recipient, GFR measures, imaging of the kidneys and the urinary tract, cardiac testing, and other tests

834 depending on the medical history. This is because, the donor's short and long-term well-being after

835 donation remains a first priorityPre-emptive transplantation (kidney transplantation before even

836 initiating dialysis) may offer several benefits to ESKD patients but its impacts remain under

837 evaluation [200]. The half-life of a transplanted kidney is <20 years, making these patients also potential

838 candidates for CKD treatments during their life span [201]. For example, recurrent glomerulonephritis is

839 an unpredictable complication that can have a negative impact on graft outcome [202].

840

841 **[H2]Conservative treatment/palliative care**

842 Kidney replacement therapy may not be available or affordable but it may also not be advisable for

843 medical reasons. Especially in very old ESKD patients, dialysis may neither increase life span nor

844 improve quality of life (QOL) [203-205]: in such cases palliative (trying to control the symptoms of uremia

845 affecting QOL [206]) and education starting at CKD G4 (aimed at explaining comorbidity management)

846 may be appropriate. Withdrawal from dialysis is a related issue and is common in very old

847 hemodialysis patients [207].

849   **[H1] Quality of life**

850   CKD-related symptoms increase along CKD progresses and are key drivers of poor QOL in patients

851   with CKD and ESRKD [208-210]. In contrast, symptoms rapidly improve upon kidney transplantation.

852   Symptoms are most severe in dialysis patients, who frequently report fatigue, nausea, dyspnea,

853   anorexia, pruritus, restless legs, and cramps [211]. Pain is especially common: in a survey of 205

854   prevalent patients on hemodialysis, approximately 25% had "severe" pain during the 24h preceding

855   the interview, and an additional 12% had "moderate pain" [212]. Mental illness including depression

856   and anxiety are also common [213], but are understudied among people with CKD. Unfortunately,

857   clinical and epidemiological characteristics associated with the presence, severity, onset and

858   remission of uremic symptoms are incompletely described; their pathophysiology is poorly

859   understood; and few drugs have been approved by regulatory authorities for their treatment [214].

860   Comorbidity and complications of CKD also substantially contribute to the reduced QOL in

861   CKD patients. In some cases (e.g. anemia), effective treatments are available. In others, treatment is

862   technically possible but has significant limitations, and treatment itself frequently causes additional

863   symptoms and morbidity (e.g. dialytic management of hypervolemia). Despite the best efforts of

864   clinicians, interactions between complications and their treatments can further compromise QOL for

865   patients (e.g. volume overload resulting from sodium bicarbonate treatment of acidosis).

866   Management of multiple comorbid conditions is already complex in patients with normal kidney

867   function [215]; the situation is even more challenging in people with CKD, where the pathophysiology

868   and optimal treatment of common coexisting conditions may differ from the general population (e.g.

869   statins for coronary disease in dialysis patients). Lack of knowledge about how to prioritize and

870   manage comorbid conditions undoubtedly contributes to the lower QOL in CKD patients through

871   multiple mechanisms – including drug-drug and drug-condition interactions; pill burden; and

872   decisional conflict for patients.

873   Dialysis is an effective life-support treatment but has many limitations in addition to those

874   mentioned above. Key challenges for hemodialysis that specifically compromise QOL include poor

875 functional status (driven in part by procedure-related immobilisation, uremia-related malnutrition,

876 and muscle wasting), the intrusive and time-consuming nature of the treatment, and vascular access

877 infection and dysfunction [216]. Instruction for some home-based, low intensity physicial exercise can

878 improve physical performance and QOL in patients on hemodialysis [217]. Peritoneal dialysis also poses

879 significant challenges for QOL including gastrointestinal distension, hernias, and chronic volume

880 overload. Both forms of dialysis make employment difficult and both are associated with a high

881 prevalence of infectious complications and undue pill burden. Some studies suggest that peritoneal

882 dialysis is associated with slightly better QOL than hemodialysis [218], but it is possible that this

883 observation is confounded by patient characteristics [219]. Home dialysis strategies are constantly

884 improving and are becoming possible tools to improve QOL [220]. Kidney transplantation is associated

885 with substantially better QOL than either form of dialysis [221], but even recipients with good graft

886 function must face CKD-related symptoms as well as complications of immunosuppression and other

887 treatments.

888 Recent emphasis on patient-centred research should help to improve QOL for people with

889 CKD by increasing the likelihood that important but understudied issues such as symptom control are

890 studied and new solutions are identified. In addition, findings from patient-centred research should

891 help to drive uptake of patient-centred care at the bedside, especially if supported by patient-

892 reported outcomes [222]. Such paradigm shifts should help to prioritize the management of patient-

893893 important issues such as reduced QOL.

894894

895 [H1] Outlook

896 There are many unmet medical needs in nephrology as a specialty and improving and refining our

897 understanding of disease mechanisms in common and rarer conditions is lacking, as are novel

898 therapies to treat rarer and common causes of kidney disease progression and a culture of curiosity

899 and clinical trials that advance the field [37]. Key areas are to improve the identification of CKD and to

900 reduce CKD risk factors, to improve the understanding of causes and consequences of CKD, to

901 improve outcomes with current knowledge, and finally to develop and test new therapeutic

902 strategies [37]. Here, we highlight eight promising domains expected to produce significant impact on

903 CKD management and outcomes.

904904

905 [H2]How genetic kidney disease contributes to CKD

906 Genetic abnormalities were identified in 20% of CKD cases in children, adolescents, and young adults.

907 Next generation sequencing have unveiled the extreme genetic heterogeneity of kidney disease. For

908 example more than 40 different genes were discovered as possible causes of steroid-resistant

909 nephrotic syndrome [142]. This requires implementation of current diagnostic strategies that go beyond

910 th renal biopsy and open to personalized diagnosis and treatments [142]. In addition, first genetic

911 modifiers of CKD progression such as *APOL1* or *UMOD* have been identified in older adults. CKD in

912 adults may also relate to (genetically- or environmentally-defined) low nephron endowment or AKI

913 episodes early in life, e.g. as early as during neonatal (intensive) care. Thus, CKD in adults, often

914 classified by a single diagnosis, may often be the consequence of several components accumulating

915 with time, a conclusion having important implications for the design of CKD trials, e.g. in prevalent

916 entities such as "diabetic nephropathy". Progress will require identifying the cause(s) of CKD and

917 dissecting modifiable from non-modifiable drivers of CKD progression as well as specific

918 pathophysiological mechanisms that might help to define more homogeneous patient subgroups.

919 The identification of such subgroups is a prerequisite to conducting more targeted clinical trials,

920 which require fewer participants and increase the possibility to identify appropriate drugs for

921 different subtypes of patients. Patient heterogeneity is considered one of the main reasons why

922 clinical trials in nephrology commonly fail [223]. Genetic investigations might therefore not only hold

923 promise for individual patients, for example by facilitating the diagnosis of a monogenic disease with

924 potential implications for individualized treatment, but might also improve classification and

925 ultimately treatment and/or prevention in groups of patients [224]. The study of the genetic

926 predisposition to kidney diseases has made major progress over the past decade. For the first time,

927 researchers have been able to carry out genome-wide screens to study complex kidney diseases, to

928 which genetic susceptibility variants in many genes, as well as environmental factors, contribute.

929 Genome-wide association studies (GWAS) have emerged as an important method to map risk loci for

930 complex dis- eases by investigating the association of genetic markers across the genome with the

931 disease of interest. We can predict that the list of genetic forms of CKD will exponentially increase

932 together with our understanding of the genetic component of kidney function in health and disease

933933 [224].

934934

935 **[H2]Biomarkers for CKD management**

936 As discussed, using serum creatinine-based diagnosis implies diagnosis as late as CKD G3, leaving a

937 small window of opportunity for modulating CKD progression. Earlier identification CKD with

938 biomarkers that can also predict CKD progression would help to initiate nephroprotective

939 interventions [37]. Most attractive would be a marker of nephron number. Defining nephron number at

940 birth would display low nephron endowment and help to dissect it from injury- or ageing-related

941 nephron loss later in life. A marker of nephron number would detect CKD G2 and could serve as an

942 end point parameter for clinical trials to quantify nephro-protective effects or drug toxicity. However,

943 identifying a clinically applicable biomarker of nephron number in serum or urine has been

944 unsuccessful so far. Biomarkers do not clearly discriminate nephron number from the compensatory

945 increase in mass of remnant nephrons upon injury (remnant nephron hypertrophy). Imaging studies

946 with tracers or the combination of imaging with kidney biopsy indicating the number of glomeruli

947 and even SNGFR are promising as a proof-of-concept [85, 225].

948

949 **[H2]Separating triggers of nephron loss from CKD progression**

950 Congenital low nephron endowment, obesity, and AKI/CKD-related nephron loss imply

951 hyperfiltration and hypertrophy of the remnant nephrons, which in turn promote secondary FSGS

952 and further nephron loss. Interstitial fibrosis most likely represents matrix replacement of lost

953 nephrons, thereby stabilizing the remnant nephrons. Whether fibrosis itself contributes to nephron

954 loss remains under debate and several antifibrotic drugs are under study to test this concept [226, 227].

955 Dissecting the relative contribution of nephron injury, wound healing, and compensatory

956 hyperfiltration remains notoriously difficult in clinical practice. Finding ways to define their relative

957 contribution and selectively target these mechanisms in a personalized manner remains a challenge

958958 for the following years.

959959

960 **[H2] Modifying CKD progression**

961 Among the many ideas on how to potentially modulate CKD progression some accumulated a large

962 fundament of experimental evidence but still await successful validation in human RCTs (e.g.

963 protecting nephron loss by modulating kidney fibrosis) [228]. In contrast, the idea to retard CKD

964 progression with urate-lowering therapies already showed promising results in smaller trials and the

965 results of ongoing multicenter RCT are eagerly awaited [229]. In contrast, the nuclear factor (erythroid-

966 derived 2)-like (NRF)-2 agonist bardoxolone or folic acid supplementation have shown

967 nephroprotective effects in RCTs in some populations but their mechanisms-of-action are not yet

968 fully understood [182, 230,231].

969969

970 **[H2]Nephrogenesis and regeneration**

971 Given the significant hurdles preventing widespread use of renal transplantation, Current work is

972 exploring whether the transfer of autologous stem (progenitor) cells, stromal cells or other cell types

973 can support the regeneration of injured nephrons (FIG. 8). For this to be a viable option, a growing

974 research field is trying to unravel the physiology and pathophysiology of the nephron's intrinsic

975 capacity to regenerate.

976 Several studies have identified possible drugable targets to specifically enhance nephron

977 regeneration with pharmacologic intervention to prevent nephron loss in AKI and CKD [232]. In

978 particular, targeting parietal epithelial cells that can act as progenitor for podocytes, to promote

979 their differentiation into fully functional podocytes and/or to block their excessive proliferation and

980 matrix production can promote remission of glomerular disorders [233-235]. In addition, enhancing

981 tubular regeneration by promoting tubular epithelial cell proliferation can reduce the occurrence of

982 CKD after AKI [234, 236]. Although in vivo experimental studies appear promising, no clinical trials are

983 available yet [233-235]. Finally, numerous Inhibitors of maladaptive repair induced improved tissue

984 structure and even function in experimental models of CKD. Several phase 1-2 clinical trials were

985 started but up to now, but none progressed beyond phase 2 [237]. However, other new antifibrotic

986 drugs display are currently being tested in clinical trials [234, 237,238].

987 Regenerative medicine is also being explored for treatment of kidney disorders. Therapeutic

988 properties mesenchymal stroma cells (MSC), a population of well-characterized, easily obtainable

989 cells with effective in numerous but not all experimental models of CKD [239, 240]. The underlying

990 mechanisms of action of the MSC have been extensively described and consist essentially in

991 immunomodulatory and paracrine effects. Similarly, numerous experimental studies reported

992 improvement of kidney function and/or structure by using injection of human renal progenitors [232-

993 236]. However, the translation of preclinical studies into robust, effective, and safe patient therapies

994 remains limited [233, 234,237].

995 Finally, the generation of 3D organ-buds termed 'organoids' from human induced pluripotent stem

996 cells and embryonic stem cells was achieved also for the kidney; these organoids consist of a variety

997 of renal cell types in vitro that mimic organs in vivo [241, 242]. The organoid bears great potential in the

998 study of human diseases in vitro, especially when combined with CRISPR/Cas9-based genome-editing

999 [243, 244]. However, the complexity of kidney structure and function is yet far from being reproduced for

1000 the purpose of clinical use for renal replacement therapy and the question if and when this will be

1001 eventually possible is still open.

1002

1003 **[H2]Animal models and RCT design**

1004   Innovative approaches to better link translational research to clinical trial findings will need to start

1005   with well-defined human genotypes and phenotypes to identify molecular targets, which may (or

1006   may not) subsequently be validated in animal models. Selecting such animal models for validation

1007   should be based on models that recapitulate CKD progression in humans and applying identical end

1008   points in subsequent clinical trials. This may include mice with identical pathogenic mutations as in

1009   human genetic kidney disease as being available for Alport syndrome, mouse models with a partial

1010   human immune system, or eventually experimentation in pigs or primates to close gaps between

1011   preclinical and clinical trials [245, 246].

1012   In addition, trial design may be improved upon reconsidering disease definitions, avoiding

1013   add-on designs using drugs with redundant mechanisms-of-action, preselecting patients with drug

1014   mechanisms-related biomarkers, and of study end points that better predict CKD progression to

1015   ESKD. For example, in order to test efficacy of the C5a receptor inhibitor avacopan in ANCA vasculitis

1016   the CLEAR trial at first avoided the usual add-on standard of care approach and compared instead

1017   avacopan plus low-dose steroids versus placebo plus high dose steroids on top of either

1018   cyclophosphamide or rituximab [247]. This way it was proven that avacopan is effective in replacing

1019   high-dose glucocorticoids in treating vasculitis.

1020

1021   **[H2]Limiting cardiovascular morbidity and mortality**

1022   Targeting the association of CKD with cardiovascular morbidity and mortality will require more

1023   functional studies in animals and humans to identify molecular targets potentially suitable for

1024   therapeutic interventions [37]. Controlling hyperlipidemia with PCSK9 inhibitors, suppressing systemic

1025   inflammation with innovative anti-inflammatory drugs, modulating the intestinal microbiota, or

1026   directly modulating vascular calcificaton and cardiac fibrosis may offer new solutions for this eminent

1027   problem in the future.

1028

1029   **[H2]Translation of advances into daily practice**

1030   The ever growing complexity of kidney biopsy reading, lab diagnostics, and the increasing need for

1031   genetic testing will require centers of excellence with sufficient resources to meet the diagnostic

1032   demands. The same may apply to upcoming costly therapies, where patient selection is of particular

1033   importance. Educational efforts are also needed to alert patients and general physicians to the

1034   increasing number of more affordable therapeutic options for CKD patients with diabetes, such as

1035   SGLT2 inhibitors. Finally, national CKD registries and treatment guidelines advocate awareness in the

1036   public, among health care providers, and decision takers, which can generate important support for

1037 implementation of standards [37]. Global guidelines created by the KDIGO initiative have become

1038 instrumental in this process starting from a global definition of CKD stages up to defining standards

1039 for the management of CKD complications (Box 3). In addition, global initiatives on CKD launched by

1040 the International Society of Nephrology define knowledge gaps in CKD and propose how to address

1041 them in the future [37].

1042

1049

1050 **Contributions.** P.R., G.R., R.G., A.L., K.J.J., M.T., Z.M., C.W., and H.J.A. all wrote parts of the

1051 manuscript.

1052

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)	• Low nephron endowment at birth (low birth weight, fetal dysmaturity)
	• Obstructive uropathy
	• Systemic vasculitis
	• Hyperhomocysteinemia
• Malignancy (especially lymphocyte and plasma cell disorders such as multiple myeloma)	
• Congenital renal abnormalities (CAKUT, vesico-ureteric reflux)	
• Episodes of acute kidney injury	

1077   **Box 2. Biochemical and serologic tests useful for defining causes of CKD**

1078   **[H1]*Auto-immune disease***

1079   - Fluorescent anti-nuclear antibody, anti-dsDNA antibody, anti-phospholipaseA2 receptor

1080   antibody, anti-GBM antibody, anti-neutrophil cytoplasmic antibody, anti-phospholipid

1081   antibody

1082   - Serum hemolytic complement activity (C'H50), serum C3 and C4 levels, cryoimmunoglobulins

1083   **[H1]*Malignancy***

1084   - Serum free light chains, serum or urinary immunofixation (multiple myeloma)

1085   - Serum albumin, phosphorous, total proteins and albumin/globulin ratio

1086   **[H1]*Infections***

1087   - Human Immunodeficiency Virus, hepatitis B virus, hepatitis C virus serology, CD4+ T cell

1088   counts, urine, blood cultures, anti-streptococcal antibody tests

1089   **[H1]*Monogenetic kidney disease***

1090   - Serum or urinary enzymes, glycolipids

1091   - Genetic testing using next generation and Sanger sequencing

1092

Box 3. Key strategies to managing CKD complications

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

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)

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

1118   analogues are no longer recommended for routine use unless secondary

1119   hyperparathyroidism in CKD G4-G5 is severe and progressive

1120   • For patients with CKD G5D PTH-lowering therapy calcimimetics, calcitriol, or vitamin D

1121   analogs are recommended

1122   • Consider patients with vascular calcifications at high risk for cardiovascular disease; avoid

1123   calcium-based phosphate binders in these patients, limit dietary phosphate intake.

1124   **[H1]Hyperlipidemia** [249]

1125   • Adults >50y with CKD should receive a statin; when eGFR <60ml/min, statin or

1126   statin/ezetimibe combination should be given

1127   • Adults <50y with CKD and other cardiovascular risk factors should receive a statin

1128   **[H1]Metabolic acidosis**

1129   • Oral bicarbonate can be used to correct mild metabolic acidosis

1130   **[H1]Chronic hyperkalemia**

1131   • Dietary restriction, loop diuretics, potassium-binding resins such as patiromer or dose

1132

1133

1134

1135

1136

1137

1138

1139

1140

1141

adjust
ments
of
RAS
inhibit
ors
and
aldost
erone
antag
onists
250

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

1194   can also influence risk, as can infections (bacterial, parasitic, viral). Severe genetic defects that lead to

1195   FSGS, Alport syndrome, cysts and atypical hemolytic uremic syndrome typically become evident early

1196   in life, whereas moderate genetic defects (such as mutation in *UMOD*) can become evident in

1197   adulthood. Genetic variants in genes such as *APOL1* can modify the course of diseases such as lupus

1198   nephritis.

1199

1200   **Figure 5. Injury, hyperfiltration and hypertrophy of the nephron.** A | In response to nephron loss,

1201   single nephron hyperfiltration induces an increase in nephron size as a compensatory mechanism to

1202   maintain overall renal function. Accordingly, podocytes need to undergo hypertrophy to maintain the

1203   filtration barrier of the increasing dimensions of the filtration surface. However, podocyte

1204   hypertrophy is limited; beyond a certain threshold, barrier dysfunction first manifests as mild to

1205   moderate proteinuria. At later stages the increasing podocyte shear stress promotes podocyte

1206   detachment. Parietal epithelial cells (PEC) host putative podocyte progenitors but proteinuria and

1207   potentially other factors inhibit their potential to replace lost podocytes and rather promote scar

1208   formation, i.e. focal segmental glomerulosclerosis (FSGS). B | Hyperfiltration and proteinuria both

1209   imply an increased reabsorption work load for proximal tubules. Activated tubular cells secrete pro-

1210   inflammatory mediators that promote interstitial inflammation. Together with the progression from

1211   FSGS to global glomerulosclerosis the inflammatory microenvironment of the tubulointerstitium

1212   promotes tubular atrophy and interstitial fibrosis. Scar formation is associated with vascular

1213   rarefication and ischemia. The remnant nephrons have to further increase in size to meet the

1214   filtration demands, which accelerates the aforementioned mechanisms of CKD progression in a

1215   vicious circle.

1216   **Figure 6. The earlier-the-better: renal outcome depending on when starting renin-angiotensin**

1217   **system (RAS) blockade in Alport Syndrome.** As shown, the time to renal replacement therapy was

1218   longest for those who started RAS inhibition early, at onset of microhematuria (usually at birth) or

1219   microalbuminuria (30-300 mg protein per day or per gram creatinine). Delaying until

1220   macroproteinuria (>0.3g/day or per gram creatinine (green curve)) or CKD G3/4 has been established

1221   considerably shortens the time to renal replacement. Untreated patients (red curve) are relatives to

1222 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).

1223

1224

1225

1226   **Figure 7. Access for hemodialysis or peritoneal dialysis. A |** Arteriovenous fistulae are created by

1227   surgical anastomosis of a peripheral artery with a larger subcutaneous vein, e.g. at the forearm. The

1228   increased flow and perfusion pressure leads to structural modifications in the draining vein allowing

1229   repetitive venous puncture for hemodialysis. Sometimes declining blood flow to the hand and fingers

1230   (steal phenomonen), compensatory increases in cardiac output or aneurysm formation cause

1231   problems and require surgical correction. **B |** Arteriovenous grafts may become necessary when the

1232   patient`s vascular status does not allow to build a fistula. Polytetrafluoroethylene grafts are mostly

1233   used and can be repetitively punctured for hemodialysis. Common problems are sterile inflammatory

1234   postimplantation syndromes or prosthetic graft infections causing bacterial sepsis. **C |** Central

1235   venous catheters become necessary when immediate initiation of renal replacement therapy is

1236   needed up to when a fistula or graft implant becomes ready for use. Such catheters may remain the

1237   last vascular access option for patients in which the vascular or cardiac status does not allow fistula

1238   or graft placement. Catheter infections or thrombotic complications remain constant concerns.

1239   Peritoneal dialysis requires placement of a transcutaneous catheter into the peritoneal cavity. This

1240   catheter allows fills, drains and refills of dialysate while the peritoneum serves as exchange

1241   membrane with the uremic blood. Fluid drains and refills with fresh dialysate are needed in regular

1242   intervals, usually 4 times a day.

1243

1244   **Figure 8. Targeting kidney regeneration.** In the future, it may be possible to target kidney

1245   regeneration and maladaptive repair to minimize the loss of injured nephrons and to protect the

1246 remnant nephrons. Here, the most promising arenas of research include: 1. Enhancing podocyte

1247 regeneration. This aim may be achieved by drugs that promote differentiation into podocyte of

1248 parietal epithelial cell (PEC) progenitors of the Bowman's capsule and/or blocking their excessive

1249 proliferation. 2. Blocking fibrosis and/or maladaptive repair by inhibiting fibroblast expansion. 3.

1250 Enhancing tubular regeneration by blocking maladaptive repair and/or enhancing tubular cell

1251 proliferation [233-238].

1252

1253 **Figure 9. Cell therapy and organoids as potential tools in CKD research and therapy.** (A) Injection of

1254 two cell types, mesenchymal stromal cells and renal progenitors, were reported as possible tools for

1255 cell therapy of CKD, improving kidney function and structure in animal models. Numerous phase 1-2

1256 clinical trials are ongoing. Several mechanisms were proposed to explain the beneficial effects

1257 observed, mostly based on secretion of paracrine factors and/or microvesicles. For renal progenitors

1258 also direct engraftment in the injured tissue was reported. (B) Kidney organoids were generated in

1259 vitro starting from induced pluripotent stem cells (iPSC) and embryonic stem cells (ESC) and used for

1260 testing of drug toxicity and modeling of kidney diseases, with or without manipulation using

1261 Crispr/Cas and other genome editing strategies.

1262

1263

1264

1265

1266

1267

1268

1269

1270

1271

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

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

1274

1275

1276

1277

1278

1279

1280

References

1281 **References**

1282   1.   Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical
1283   practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*
1284   *Suppl* **3**, 1-150 (2013).
1285   2.   Glassock, R., Delanaye, P. & El Nahas, M. An Age-Calibrated Classification of Chronic Kidney
1286   Disease. *JAMA* **314**, 559-60 (2015).
1287   3.   Levey, A.S., Inker, L.A. & Coresh, J. Chronic Kidney Disease in Older People. *JAMA* **314**, 557-8
1288   (2015).
1289   4.   Poggio, E.D. et al. Demographic and clinical characteristics associated with glomerular
1290   filtration rates in living kidney donors. *Kidney Int* **75**, 1079-87 (2009).
1291   5.   Pottel, H., Hoste, L., Yayo, E. & Delanaye, P. Glomerular Filtration Rate in Healthy Living
1292   Potential Kidney Donors: A Meta-Analysis Supporting the Construction of the Full Age
1293   Spectrum Equation. *Nephron* **135**, 105-119 (2017).
1294   6.   Glassock, R.J. & Rule, A.D. The implications of anatomical and functional changes of the aging
1295   kidney: with an emphasis on the glomeruli. *Kidney Int* **82**, 270-7 (2012).
1296   7.   Hallan, S.I. et al. Age and association of kidney measures with mortality and end-stage renal
1297   disease. *JAMA* **308**, 2349-60 (2012).
1298   8.   Warnock, D.G., Delanaye, P. & Glassock, R.J. Risks for All-Cause Mortality: Stratified by Age,
1299   Estimated Glomerular Filtration Rate and Albuminuria. *Nephron* (2017).
1300   9.   De Broe, M.E., Gharbi, M.B., Zamd, M. & Elseviers, M. Why overestimate or underestimate
1301   chronic kidney disease when correct estimation is possible? *Nephrol Dial Transplant* **32**,
1302   ii136-ii141 (2017).
1303   10.   Denic, A., Glassock, R.J. & Rule, A.D. Structural and Functional Changes With the Aging
1304   Kidney. *Adv Chronic Kidney Dis* **23**, 19-28 (2016).
1305   11.   DALYs, G.B.D. & Collaborators, H. Global, regional, and national disability-adjusted life-years
1306   (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a
1307   systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1603-1658
1308   (2016).
1309   12.   Jager, K.J. & Fraser, S.D.S. The ascending rank of chronic kidney disease in the global burden
1310   of disease study. *Nephrol Dial Transplant* **32**, ii121-ii128 (2017).
1311   13.   Mortality, G.B.D. & Causes of Death, C. Global, regional, and national age-sex specific all-
1312   cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis
1313   for the Global Burden of Disease Study 2013. *Lancet* **385**, 117-71 (2015).
1314   14.   Thomas, B. et al. Global Cardiovascular and Renal Outcomes of Reduced GFR. *J Am Soc*
1315   *Nephrol* **28**, 2167-2179 (2017).
1316   15.   Zhang, L. et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*
1317   **379**, 815-22 (2012).
1318   16.   Arora, P. et al. Prevalence estimates of chronic kidney disease in Canada: results of a
1319   nationally representative survey. *CMAJ* **185**, E417-23 (2013).
1320   17.   White, S.L., Polkinghorne, K.R., Atkins, R.C. & Chadban, S.J. Comparison of the prevalence
1321   and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI)
1322   and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the
1323   AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis* **55**, 660-70
1324   (2010).
1325   18.   Levey, A.S. & Coresh, J. Chronic kidney disease. *Lancet* **379**, 165-80 (2012).
1326   19.   Girndt, M., Trocchi, P., Scheidt-Nave, C., Markau, S. & Stang, A. The Prevalence of Renal
1327   Failure. Results from the German Health Interview and Examination Survey for Adults, 2008-
1328   2011 (DEGS1). *Dtsch Arztebl Int* **113**, 85-91 (2016).
1329   20.   Bruck, K. et al. CKD Prevalence Varies across the European General Population. *J Am Soc*
1330   *Nephrol* **27**, 2135-47 (2016).

1331   21.   Fraser, S.D. et al. Exploration of chronic kidney disease prevalence estimates using new
1332   measures of kidney function in the health survey for England. *PLoS One* **10**, e0118676 (2015).
1333   22.   Glassock, R.J., Warnock, D.G. & Delanaye, P. The global burden of chronic kidney disease:
1334   estimates, variability and pitfalls. *Nat Rev Nephrol* **13**, 104-114 (2017).
1335   23.   Stanifer, J.W., Muiru, A., Jafar, T.H. & Patel, U.D. Chronic kidney disease in low- and middle-
1336   income countries. *Nephrol Dial Transplant* **31**, 868-74 (2016).
1337   24.   Stanifer, J.W. et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a
1338   systematic review and meta-analysis. *Lancet Glob Health* **2**, e174-81 (2014).
1339   25.   Ene-Iordache, B. et al. Chronic kidney disease and cardiovascular risk in six regions of the
1340   world (ISN-KDDC): a cross-sectional study. *Lancet Glob Health* **4**, e307-19 (2016).
1341   26.   Hill, N.R. et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-
1342   Analysis. *PLoS One* **11**, e0158765 (2016).
1343   27.   Jha, V. et al. Chronic kidney disease: global dimension and perspectives. *Lancet* **382**, 260-72
1344   (2013).
1345   28.   Charlton, J.R., Springsteen, C.H. & Carmody, J.B. Nephron number and its determinants in
1346   early life: a primer. *Pediatr Nephrol* **29**, 2299-308 (2014).
1347   29.   Khalsa, D.D., Beydoun, H.A. & Carmody, J.B. Prevalence of chronic kidney disease risk factors
1348   among low birth weight adolescents. *Pediatr Nephrol* **31**, 1509-16 (2016).
1349   30.   Gifford, F.J., Gifford, R.M., Eddleston, M. & Dhaun, N. Endemic Nephropathy Around the
1350   World. *Kidney Int Rep* **2**, 282-292 (2017).
1351   31.   Glaser, J. et al. Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural
1352   Communities: The Case for Heat Stress Nephropathy. *Clin J Am Soc Nephrol* **11**, 1472-83
1353   (2016).
1354   32.   Jayasumana, C. et al. Chronic interstitial nephritis in agricultural communities: a worldwide
1355   epidemic with social, occupational and environmental determinants. *Nephrol Dial Transplant*
1356   **32**, 234-241 (2017).
1357   33.   ESPN/ERA-EDTA Registry. Annual Report. *www.espn-reg.org/index.jsp* *(last accessed April
1358   2017).* (2014).
1359   34.   Chesnaye, N. et al. Demographics of paediatric renal replacement therapy in Europe: a report
1360   of the ESPN/ERA-EDTA registry. *Pediatr Nephrol* **29**, 2403-10 (2014).
1361   35.   Saran, R. et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney
1362   Disease in the United States. *Am J Kidney Dis* **69**, A7-A8 (2017).
1363   36.   Harambat, J., van Stralen, K.J., Kim, J.J. & Tizard, E.J. Epidemiology of chronic kidney disease
1364   in children. *Pediatr Nephrol* **27**, 363-73 (2012).
1365   37.   Levin, A. et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care,
1366   research, and policy. *Lancet* (2017).
1367   38.   Bello, A.K. et al. Assessment of Global Kidney Health Care Status. *JAMA* **317**, 1864-1881
1368   (2017).
1369   39.   Liyanage, T. et al. Worldwide access to treatment for end-stage kidney disease: a systematic
1370   review. *Lancet* **385**, 1975-82 (2015).
1371   40.   Bertram, J.F., Douglas-Denton, R.N., Diouf, B., Hughson, M.D. & Hoy, W.E. Human nephron
1372   number: implications for health and disease. *Pediatr Nephrol* **26**, 1529-33 (2011).
1373   41.   Brenner, B.M., Meyer, T.W. & Hostetter, T.H. Dietary protein intake and the progressive
1374   nature of kidney disease: the role of hemodynamically mediated glomerular injury in the
1375   pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal
1376   disease. *N Engl J Med* **307**, 652-9 (1982).
1377   42.   Hostetter, T.H., Olson, J.L., Rennke, H.G., Venkatachalam, M.A. & Brenner, B.M.
1378   Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J
1379   Physiol* **241**, F85-93 (1981).
1380   43.   Benghanem Gharbi, M. et al. Chronic kidney disease, hypertension, diabetes, and obesity in
1381   the adult population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD. *Kidney
1382   Int* **89**, 1363-71 (2016).

1383   44.   Ruggenenti, P., Cravedi, P. & Remuzzi, G. Mechanisms and treatment of CKD. *J Am Soc*
1384   *Nephrol* **23**, 1917-28 (2012).
1385   45.   Laouari, D. et al. TGF-alpha mediates genetic susceptibility to chronic kidney disease. *J Am*
1386   *Soc Nephrol* **22**, 327-35 (2011).
1387   46.   Helal, I., Fick-Brosnahan, G.M., Reed-Gitomer, B. & Schrier, R.W. Glomerular hyperfiltration:
1388   definitions, mechanisms and clinical implications. *Nat Rev Nephrol* **8**, 293-300 (2012).
1389   47.   Grams, M.E. et al. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. *N*
1390   *Engl J Med* **374**, 411-21 (2016).
1391   48.   Mueller, T.F. & Luyckx, V.A. The natural history of residual renal function in transplant
1392   donors. *J Am Soc Nephrol* **23**, 1462-6 (2012).
1393   49.   D'Agati, V.D. et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and
1394   pathogenesis. *Nat Rev Nephrol* **12**, 453-71 (2016).
1395   50.   Park, S. et al. Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of
1396   Gestational Hyperfiltration. *Clin J Am Soc Nephrol* (2017).
1397   51.   Tonneijck, L. et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance,
1398   and Treatment. *J Am Soc Nephrol* **28**, 1023-1039 (2017).
1399   52.   Denic, A. et al. The Substantial Loss of Nephrons in Healthy Human Kidneys with Aging. *J Am*
1400   *Soc Nephrol* **28**, 313-320 (2017).
1401   53.   Hodgin, J.B. et al. Glomerular Aging and Focal Global Glomerulosclerosis: A Podometric
1402   Perspective. *J Am Soc Nephrol* **26**, 3162-78 (2015).
1403   54.   Kriz, W. & Lemley, K.V. The role of the podocyte in glomerulosclerosis. *Curr Opin Nephrol*
1404   *Hypertens* **8**, 489-97 (1999).
1405   55.   Kriz, W. & Lemley, K.V. A potential role for mechanical forces in the detachment of podocytes
1406   and the progression of CKD. *J Am Soc Nephrol* **26**, 258-69 (2015).
1407   56.   Benigni, A., Gagliardini, E. & Remuzzi, G. Changes in glomerular perm-selectivity induced by
1408   angiotensin II imply podocyte dysfunction and slit diaphragm protein rearrangement. *Semin*
1409   *Nephrol* **24**, 131-40 (2004).
1410   57.   Rizzo, P. et al. Nature and mediators of parietal epithelial cell activation in
1411   glomerulonephritides of human and rat. *Am J Pathol* **183**, 1769-78 (2013).
1412   58.   Abbate, M. et al. Transforming growth factor-beta1 is up-regulated by podocytes in response
1413   to excess intraglomerular passage of proteins: a central pathway in progressive
1414   glomerulosclerosis. *Am J Pathol* **161**, 2179-93 (2002).
1415   59.   Abbate, M., Zoja, C. & Remuzzi, G. How does proteinuria cause progressive renal damage? *J*
1416   *Am Soc Nephrol* **17**, 2974-84 (2006).
1417   60.   Peired, A. et al. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. *J*
1418   *Am Soc Nephrol* **24**, 1756-68 (2013).
1419   61.   Smeets, B. et al. Parietal epithelial cells participate in the formation of sclerotic lesions in
1420   focal segmental glomerulosclerosis. *J Am Soc Nephrol* **22**, 1262-74 (2011).
1421   62.   Schnaper, H.W. The Tubulointerstitial Pathophysiology of Progressive Kidney Disease. *Adv*
1422   *Chronic Kidney Dis* **24**, 107-116 (2017).
1423   63.   Kaissling, B., Lehir, M. & Kriz, W. Renal epithelial injury and fibrosis. *Biochim Biophys Acta*
1424   **1832**, 931-9 (2013).
1425   64.   Brenner, B.M., Garcia, D.L. & Anderson, S. Glomeruli and blood pressure. Less of one, more
1426   the other? *Am J Hypertens* **1**, 335-47 (1988).
1427   65.   de Jong, F., Monuteaux, M.C., van Elburg, R.M., Gillman, M.W. & Belfort, M.B. Systematic
1428   review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension* **59**,
1429   226-34 (2012).
1430   66.   Low Birth, W. & Nephron Number Working, G. The Impact of Kidney Development on the Life
1431   Course: A Consensus Document for Action. *Nephron* **136**, 3-49 (2017).
1432   67.   Luyckx, V.A. & Brenner, B.M. Birth weight, malnutrition and kidney-associated outcomes--a
1433   global concern. *Nat Rev Nephrol* **11**, 135-49 (2015).

1434 68. White, S.L. et al. Is low birth weight an antecedent of CKD in later life? A systematic review of
1435 observational studies. *Am J Kidney Dis* **54**, 248-61 (2009).
1436 69. Hirano, D. et al. Association between low birth weight and childhood-onset chronic kidney
1437 disease in Japan: a combined analysis of a nationwide survey for paediatric chronic kidney
1438 disease and the National Vital Statistics Report. *Nephrol Dial Transplant* **31**, 1895-1900
1439 (2016).
1440 70. Ruggajo, P. et al. Low Birth Weight and Risk of Progression to End Stage Renal Disease in IgA
1441 Nephropathy--A Retrospective Registry-Based Cohort Study. *PLoS One* **11**, e0153819 (2016).
1442 71. Becherucci, F., Roperto, R.M., Materassi, M. & Romagnani, P. Chronic kidney disease in
1443 children. *Clin Kidney J* **9**, 583-91 (2016).
1444 72. Luyckx, V.A. et al. A developmental approach to the prevention of hypertension and kidney
1445 disease: a report from the Low Birth Weight and Nephron Number Working Group. *Lancet*
1446 (2017).
1447 73. Keller, G., Zimmer, G., Mall, G., Ritz, E. & Amann, K. Nephron number in patients with
1448 primary hypertension. *N Engl J Med* **348**, 101-8 (2003).
1449 74. Nicolaou, N., Renkema, K.Y., Bongers, E.M., Giles, R.H. & Knoers, N.V. Genetic,
1450 environmental, and epigenetic factors involved in CAKUT. *Nat Rev Nephrol* **11**, 720-31 (2015).
1451 75. Cain, J.E., Di Giovanni, V., Smeeton, J. & Rosenblum, N.D. Genetics of renal hypoplasia:
1452 insights into the mechanisms controlling nephron endowment. *Pediatr Res* **68**, 91-8 (2010).
1453 76. Uy, N. & Reidy, K. Developmental Genetics and Congenital Anomalies of the Kidney and
1454 Urinary Tract. *J Pediatr Genet* **5**, 51-60 (2016).
1455 77. Vivante, A. & Hildebrandt, F. Exploring the genetic basis of early-onset chronic kidney
1456 disease. *Nat Rev Nephrol* **12**, 133-46 (2016).
1457 78. Eckardt, K.U. et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis,
1458 classification, and management--A KDIGO consensus report. *Kidney Int* **88**, 676-83 (2015).
1459 79. Kottgen, A. et al. Multiple loci associated with indices of renal function and chronic kidney
1460 disease. *Nat Genet* **41**, 712-7 (2009).
1461 80. Reznichenko, A. et al. UMOD as a susceptibility gene for end-stage renal disease. *BMC Med*
1462 *Genet* **13**, 78 (2012).
1463 81. Trudu, M. et al. Common noncoding UMOD gene variants induce salt-sensitive hypertension
1464 and kidney damage by increasing uromodulin expression. *Nat Med* **19**, 1655-60 (2013).
1465 82. Dummer, P.D. et al. APOL1 Kidney Disease Risk Variants: An Evolving Landscape. *Semin*
1466 *Nephrol* **35**, 222-36 (2015).
1467 83. Kruzel-Davila, E. et al. APOL1-Mediated Cell Injury Involves Disruption of Conserved
1468 Trafficking Processes. *J Am Soc Nephrol* **28**, 1117-1130 (2017).
1469 84. Beckerman, P. et al. Transgenic expression of human APOL1 risk variants in podocytes
1470 induces kidney disease in mice. *Nat Med* **23**, 429-438 (2017).
1471 85. Denic, A. et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med*
1472 **376**, 2349-2357 (2017).
1473 86. Lu, J.L. et al. Association of age and BMI with kidney function and mortality: a cohort study.
1474 *Lancet Diabetes Endocrinol* **3**, 704-14 (2015).
1475 87. Kramer, H. et al. Waist Circumference, Body Mass Index, and ESRD in the REGARDS (Reasons
1476 for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis* **67**, 62-9 (2016).
1477 88. Chang, A. et al. Lifestyle-related factors, obesity, and incident microalbuminuria: the CARDIA
1478 (Coronary Artery Risk Development in Young Adults) study. *Am J Kidney Dis* **62**, 267-75
1479 (2013).
1480 89. Ejerblad, E. et al. Obesity and risk for chronic renal failure. *J Am Soc Nephrol* **17**, 1695-702
1481 (2006).
1482 90. Foster, M.C. et al. Overweight, obesity, and the development of stage 3 CKD: the
1483 Framingham Heart Study. *Am J Kidney Dis* **52**, 39-48 (2008).
1484 91. Vivante, A. et al. Body mass index in 1.2 million adolescents and risk for end-stage renal
1485 disease. *Arch Intern Med* **172**, 1644-50 (2012).

1486   92.   Dunlop, W. Serial changes in renal haemodynamics during normal human pregnancy. *Br J*
1487   *Obstet Gynaecol* **88**, 1-9 (1981).
1488   93.   Moran, P., Baylis, P.H., Lindheimer, M.D. & Davison, J.M. Glomerular ultrafiltration in normal
1489   and preeclamptic pregnancy. *J Am Soc Nephrol* **14**, 648-52 (2003).
1490   94.   Anders, H.J., Davis, J.M. & Thurau, K. Nephron Protection in Diabetic Kidney Disease. *N Engl J*
1491   *Med* **375**, 2096-2098 (2016).
1492   95.   Vallon, V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus.
1493   *Annu Rev Med* **66**, 255-70 (2015).
1494   96.   van Bommel, E.J. et al. SGLT2 Inhibition in the Diabetic Kidney-From Mechanisms to Clinical
1495   Outcome. *Clin J Am Soc Nephrol* **12**, 700-710 (2017).
1496   97.   Anguiano Gomez, L., Lei, Y., Devarapu, S.K. & Anders, H.J. The diabetes pandemic suggests
1497   unmet needs for 'CKD with diabetes' in addition to 'diabetic nephropathy'. Implications for
1498   pre-clinical research and drug testing. *Nephrol Dial Transplant* **in press** (2017).
1499   98.   Wanner, C. et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J*
1500   *Med* **375**, 323-34 (2016).
1501   99.   Bellomo, R., Kellum, J.A. & Ronco, C. Acute kidney injury. *Lancet* **380**, 756-66 (2012).
1502   100.   Venkatachalam, M.A., Weinberg, J.M., Kriz, W. & Bidani, A.K. Failed Tubule Recovery, AKI-
1503   CKD Transition, and Kidney Disease Progression. *J Am Soc Nephrol* **26**, 1765-76 (2015).
1504   101.   Barton, A.L., Mallard, A.S. & Parry, R.G. One Year's Observational Study of Acute Kidney
1505   Injury Incidence in Primary Care; Frequency of Follow-Up Serum Creatinine and Mortality
1506   Risk. *Nephron* **130**, 175-81 (2015).
1507   102.   Eckardt, K.U. et al. Evolving importance of kidney disease: from subspecialty to global health
1508   burden. *Lancet* **382**, 158-69 (2013).
1509   103.   Lasagni, L., Lazzeri, E., Shankland, S.J., Anders, H.J. & Romagnani, P. Podocyte mitosis - a
1510   catastrophe. *Curr Mol Med* **13**, 13-23 (2013).
1511   104.   Liapis, H., Romagnani, P. & Anders, H.J. New insights into the pathology of podocyte loss:
1512   mitotic catastrophe. *Am J Pathol* **183**, 1364-74 (2013).
1513   105.   Portale, A.A. et al. Disordered FGF23 and mineral metabolism in children with CKD. *Clin J Am*
1514   *Soc Nephrol* **9**, 344-53 (2014).
1515   106.   Denburg, M.R. et al. Fracture Burden and Risk Factors in Childhood CKD: Results from the
1516   CKiD Cohort Study. *J Am Soc Nephrol* **27**, 543-50 (2016).
1517   107.   Flynn, J.T. et al. Blood pressure in children with chronic kidney disease: a report from the
1518   Chronic Kidney Disease in Children study. *Hypertension* **52**, 631-7 (2008).
1519   108.   Foley, R.N., Parfrey, P.S. & Sarnak, M.J. Clinical epidemiology of cardiovascular disease in
1520   chronic renal disease. *Am J Kidney Dis* **32**, S112-9 (1998).
1521   109.   Raschenberger, J. et al. Association of relative telomere length with cardiovascular disease in
1522   a large chronic kidney disease cohort: the GCKD study. *Atherosclerosis* **242**, 529-34 (2015).
1523   110.   Grabner, A. et al. Activation of Cardiac Fibroblast Growth Factor Receptor 4 Causes Left
1524   Ventricular Hypertrophy. *Cell Metab* **22**, 1020-32 (2015).
1525   111.   de Jager, D.J. et al. Cardiovascular and noncardiovascular mortality among patients starting
1526   dialysis. *JAMA* **302**, 1782-9 (2009).
1527   112.   De Cosmo, S., Menzaghi, C., Prudente, S. & Trischitta, V. Role of insulin resistance in kidney
1528   dysfunction: insights into the mechanism and epidemiological evidence. *Nephrol Dial*
1529   *Transplant* **28**, 29-36 (2013).
1530   113.   Cozzolino, M., Ketteler, M. & Zehnder, D. The vitamin D system: a crosstalk between the
1531   heart and kidney. *Eur J Heart Fail* **12**, 1031-41 (2010).
1532   114.   Vervloet, M. & Cozzolino, M. Vascular calcification in chronic kidney disease: different bricks
1533   in the wall? *Kidney Int* **91**, 808-817 (2017).
1534   115.   Carrero, J.J. et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease:
1535   a consensus statement from the International Society of Renal Nutrition and Metabolism
1536   (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).

1588   138.   Jin, B. et al. The spectrum of biopsy-proven kidney diseases in elderly Chinese patients.
1589   *Nephrol Dial Transplant* **29**, 2251-9 (2014).
1590   139.   Xu, D.M., Chen, M., Zhou, F.D. & Zhao, M.H. Risk Factors for Severe Bleeding Complications in
1591   Percutaneous Renal Biopsy. *Am J Med Sci* **353**, 230-235 (2017).
1592   140.   Siwy, J. et al. Noninvasive diagnosis of chronic kidney diseases using urinary proteome
1593   analysis. *Nephrol Dial Transplant* (2016).
1594   141.   Li, J., An, C., Kang, L., Mitch, W.E. & Wang, Y. Recent Advances in Magnetic Resonance
1595   Imaging Assessment of Renal Fibrosis. *Adv Chronic Kidney Dis* **24**, 150-153 (2017).
1596   142.   Becherucci, F. et al. Lessons from genetics: is it time to revise the therapeutic approach to
1597   children with steroid-resistant nephrotic syndrome? *J Nephrol* **29**, 543-50 (2016).
1598   143.   Peralta, C.A. & Estrella, M.M. Preventive nephrology in the era of "I" evidence: should we
1599   screen for chronic kidney disease? *Kidney Int* **92**, 19-21 (2017).
1600   144.   Taal, M.W. Screening for chronic kidney disease: preventing harm or harming the healthy?
1601   *PLoS Med* **9**, e1001345 (2012).
1602   145.   Moyer, V.A. & Force, U.S.P.S.T. Screening for chronic kidney disease: U.S. Preventive Services
1603   Task Force recommendation statement. *Ann Intern Med* **157**, 567-70 (2012).
1604   146.   Fink, H.A. et al. Screening for, monitoring, and treatment of chronic kidney disease stages 1
1605   to 3: a systematic review for the U.S. Preventive Services Task Force and for an American
1606   College of Physicians Clinical Practice Guideline. *Ann Intern Med* **156**, 570-81 (2012).
1607   147.   Caley, M., Chohan, P., Hooper, J. & Wright, N. The impact of NHS Health Checks on the
1608   prevalence of disease in general practices: a controlled study. *Br J Gen Pract* **64**, e516-21
1609   (2014).
1610   148.   Imai, E. et al. Kidney disease screening program in Japan: history, outcome, and perspectives.
1611   *Clin J Am Soc Nephrol* **2**, 1360-6 (2007).
1612   149.   Khwaja, A. & Throssell, D. A critique of the UK NICE guidance for the detection and
1613   management of individuals with chronic kidney disease. *Nephron Clin Pract* **113**, c207-13
1614   (2009).
1615   150.   Smith, J.M., Mott, S.A., Hoy, W.E. & International Federation of Kidney, F. Status of chronic
1616   kidney disease prevention programs: International Federation of Kidney Foundation
1617   Members 2005/2007. *Kidney Int* **74**, 1516-25 (2008).
1618   151.   Tonelli, M. et al. How to advocate for the inclusion of chronic kidney disease in a national
1619   noncommunicable chronic disease program. *Kidney Int* **85**, 1269-74 (2014).
1620   152.   Hoerger, T.J. et al. A health policy model of CKD: 2. The cost-effectiveness of
1621   microalbuminuria screening. *Am J Kidney Dis* **55**, 463-73 (2010).
1622   153.   Perkovic, V. et al. Management of patients with diabetes and CKD: conclusions from a
1623   "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int*
1624   **90**, 1175-1183 (2016).
1625   154.   Ozyilmaz, A. et al. Screening for albuminuria with subsequent screening for hypertension and
1626   hypercholesterolaemia identifies subjects in whom treatment is warranted to prevent
1627   cardiovascular events. *Nephrol Dial Transplant* **28**, 2805-15 (2013).
1628   155.   Tanaka, F. et al. Low-grade albuminuria and incidence of cardiovascular disease and all-cause
1629   mortality in nondiabetic and normotensive individuals. *J Hypertens* **34**, 506-12; discussion
1630   512 (2016).
1631   156.   Shardlow, A., McIntyre, N.J., Fluck, R.J., McIntyre, C.W. & Taal, M.W. Chronic Kidney Disease
1632   in Primary Care: Outcomes after Five Years in a Prospective Cohort Study. *PLoS Med* **13**,
1633   e1002128 (2016).
1634   157.   Grams, M.E. et al. Race, APOL1 Risk, and eGFR Decline in the General Population. *J Am Soc*
1635   *Nephrol* **27**, 2842-50 (2016).
1636   158.   Kovesdy, C.P., Furth, S.L., Zoccali, C. & World Kidney Day Steering, C. Obesity and Kidney
1637   Disease: Hidden Consequences of the Epidemic. *Can J Kidney Health Dis* **4**,
1638   2054358117698669 (2017).

1639   159.   de Galan, B.E. et al. Lowering blood pressure reduces renal events in type 2 diabetes. *J Am*
1640   *Soc Nephrol* **20**, 883-92 (2009).
1641   160.   Oellgaard, J. et al. Intensified multifactorial intervention in type 2 diabetics with
1642   microalbuminuria leads to long-term renal benefits. *Kidney Int* **91**, 982-988 (2017).
1643   161.   Perkovic, V. et al. Intensive glucose control improves kidney outcomes in patients with type 2
1644   diabetes. *Kidney Int* **83**, 517-23 (2013).
1645   162.   Gross, O. et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays
1646   renal failure and improves life expectancy. *Kidney Int* **81**, 494-501 (2012).
1647   163.   Schievink, B. et al. Early renin-angiotensin system intervention is more beneficial than late
1648   intervention in delaying end-stage renal disease in patients with type 2 diabetes. *Diabetes*
1649   *Obes Metab* **18**, 64-71 (2016).
1650   164.   Oliveira, B., Kleta, R., Bockenhauer, D. & Walsh, S.B. Genetic, pathophysiological, and clinical
1651   aspects of nephrocalcinosis. *Am J Physiol Renal Physiol* **311**, F1243-F1252 (2016).
1652   165.   Trautmann, A. et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in
1653   children: the PodoNet registry cohort. *Clin J Am Soc Nephrol* **10**, 592-600 (2015).
1654   166.   Noris, M. & Remuzzi, G. Glomerular Diseases Dependent on Complement Activation,
1655   Including Atypical Hemolytic Uremic Syndrome, Membranoproliferative Glomerulonephritis,
1656   and C3 Glomerulopathy: Core Curriculum 2015. *Am J Kidney Dis* **66**, 359-75 (2015).
1657   167.   Hildebrand, A.M., Huang, S.H. & Clark, W.F. Plasma exchange for kidney disease: what is the
1658   best evidence? *Adv Chronic Kidney Dis* **21**, 217-27 (2014).
1659   168.   Rauen, T. et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N*
1660   *Engl J Med* **373**, 2225-36 (2015).
1661   169.   Staplin, N. et al. Smoking and Adverse Outcomes in Patients With CKD: The Study of Heart
1662   and Renal Protection (SHARP). *Am J Kidney Dis* **68**, 371-80 (2016).
1663   170.   Cravedi, P., Ruggenenti, P. & Remuzzi, G. Intensified inhibition of renin-angiotensin system: a
1664   way to improve renal protection? *Curr Hypertens Rep* **9**, 430-6 (2007).
1665   171.   Schrier, R.W. et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N*
1666   *Engl J Med* **371**, 2255-66 (2014).
1667   172.   Weir, M.R. et al. Effectiveness of patiromer in the treatment of hyperkalemia in chronic
1668   kidney disease patients with hypertension on diuretics. *J Hypertens* **35 Suppl 1**, S57-S63
1669   (2017).
1670   173.   Holtkamp, F.A. et al. An acute fall in estimated glomerular filtration rate during treatment
1671   with losartan predicts a slower decrease in long-term renal function. *Kidney Int* **80**, 282-7
1672   (2011).
1673   174.   Ruggenenti, P. et al. Role of remission clinics in the longitudinal treatment of CKD. *J Am Soc*
1674   *Nephrol* **19**, 1213-24 (2008).
1675   175.   Daina, E. et al. A multidrug, antiproteinuric approach to alport syndrome: a ten-year cohort
1676   study. *Nephron* **130**, 13-20 (2015).
1677   176.   Li, K. et al. Effects of Bariatric Surgery on Renal Function in Obese Patients: A Systematic
1678   Review and Meta Analysis. *PLoS One* **11**, e0163907 (2016).
1679   177.   Guideline development, g. Clinical Practice Guideline on management of patients with
1680   diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial*
1681   *Transplant* **30 Suppl 2**, ii1-142 (2015).
1682   178.   Neal, B. et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J*
1683   *Med* (2017).
1684   179.   Zinman, B. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N*
1685   *Engl J Med* **373**, 2117-28 (2015).
1686   180.   Wanner, C., Amann, K. & Shoji, T. The heart and vascular system in dialysis. *Lancet* **388**, 276-
1687   84 (2016).
1688   181.   Rossignol, P. et al. Cardiovascular outcome trials in patients with chronic kidney disease:
1689   challenges associated with selection of patients and endpoints. *Eur Heart J* (2017).

1690   182.   Xu, X. et al. Efficacy of Folic Acid Therapy on the Progression of Chronic Kidney Disease: The
1691   Renal Substudy of the China Stroke Primary Prevention Trial. *JAMA Intern Med* **176**, 1443-
1692   1450 (2016).
1693   183.   Baigent, C. et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in
1694   patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised
1695   placebo-controlled trial. *Lancet* **377**, 2181-92 (2011).
1696   184.   Cholesterol Treatment Trialists, C. et al. Impact of renal function on the effects of LDL
1697   cholesterol lowering with statin-based regimens: a meta-analysis of individual participant
1698   data from 28 randomised trials. *Lancet Diabetes Endocrinol* **4**, 829-39 (2016).
1699   185.   Fellstrom, B.C. et al. Rosuvastatin and cardiovascular events in patients undergoing
1700   hemodialysis. *N Engl J Med* **360**, 1395-407 (2009).
1701   186.   Wanner, C. et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing
1702   hemodialysis. *N Engl J Med* **353**, 238-48 (2005).
1703   187.   Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical
1704   Practice Guideline for Anemia in Chronic Kidney Disease. . *Kidney inter., Suppl.* **2**, 279-335
1705   (2012).
1706   188.   Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO
1707   Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. .
1708   *Kidney inter., Suppl.* **2**, 337-414 (2012).
1709   189.   KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and
1710   Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) *Kidney Int*
1711   *Suppl* **7**, 1-59 (2017).
1712   190.   Sumida, K. & Kovesdy, C.P. Disease Trajectories Before ESRD: Implications for Clinical
1713   Management. *Semin Nephrol* **37**, 132-143 (2017).
1714   191.   Ricardo, A.C. et al. Influence of Nephrologist Care on Management and Outcomes in Adults
1715   with Chronic Kidney Disease. *J Gen Intern Med* **31**, 22-9 (2016).
1716   192.   Kolff, W.J. The artificial kidney. *J Mt Sinai Hosp N Y* **14**, 71-9 (1947).
1717   193.   Tordoir, J. et al. EBPG on Vascular Access. *Nephrol Dial Transplant* **22 Suppl 2**, ii88-117
1718   (2007).
1719   194.   Ravani, P. et al. Associations between hemodialysis access type and clinical outcomes: a
1720   systematic review. *J Am Soc Nephrol* **24**, 465-73 (2013).
1721   195.   Xue, H. et al. Hemodialysis access usage patterns in the incident dialysis year and associated
1722   catheter-related complications. *Am J Kidney Dis* **61**, 123-30 (2013).
1723   196.   Alencar de Pinho, N. et al. Vascular access conversion and patient outcome after
1724   hemodialysis initiation with a nonfunctional arteriovenous access: a prospective registry-
1725   based study. *BMC Nephrol* **18**, 74 (2017).
1726   197.   Wallace, E.L. et al. Catheter Insertion and Perioperative Practices Within the ISPD North
1727   American Research Consortium. *Perit Dial Int* **36**, 382-6 (2016).
1728   198.   Leurs, P., Machowska, A. & Lindholm, B. Timing of dialysis initiation: when to start? Which
1729   treatment? *J Ren Nutr* **25**, 238-41 (2015).
1730   199.   Abramowicz, D. et al. European Renal Best Practice Guideline on kidney donor and recipient
1731   evaluation and perioperative care. *Nephrol Dial Transplant* **30**, 1790-7 (2015).
1732   200.   Sebille, V. et al. Prospective, multicenter, controlled study of quality of life, psychological
1733   adjustment process and medical outcomes of patients receiving a preemptive kidney
1734   transplant compared to a similar population of recipients after a dialysis period of less than
1735   three years--The PreKit-QoL study protocol. *BMC Nephrol* **17**, 11 (2016).
1736   201.   Chang, P. et al. Living donor age and kidney allograft half-life: implications for living donor
1737   paired exchange programs. *Clin J Am Soc Nephrol* **7**, 835-41 (2012).
1738   202.   Allen, P.J. et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and
1739   allograft outcomes. *Kidney Int* (2017).

1740   203.   Carson, R.C., Juszczak, M., Davenport, A. & Burns, A. Is maximum conservative management
1741   an equivalent treatment option to dialysis for elderly patients with significant comorbid
1742   disease? *Clin J Am Soc Nephrol* **4**, 1611-9 (2009).
1743   204.   Morton, R.L. et al. Conservative Management and End-of-Life Care in an Australian Cohort
1744   with ESRD. *Clin J Am Soc Nephrol* **11**, 2195-2203 (2016).
1745   205.   Verberne, W.R. et al. Comparative Survival among Older Adults with Advanced Kidney
1746   Disease Managed Conservatively Versus with Dialysis. *Clin J Am Soc Nephrol* **11**, 633-40
1747   (2016).
1748   206.   Crail, S., Walker, R., Brown, M. & Renal Supportive Care working, g. Renal supportive and
1749   palliative care: position statement. *Nephrology (Carlton)* **18**, 393-400 (2013).
1750   207.   Birmele, B. et al. Death after withdrawal from dialysis: the most common cause of death in a
1751   French dialysis population. *Nephrol Dial Transplant* **19**, 686-91 (2004).
1752   208.   Cox, K.J., Parshall, M.B., Hernandez, S.H., Parvez, S.Z. & Unruh, M.L. Symptoms among
1753   patients receiving in-center hemodialysis: A qualitative study. *Hemodial Int* (2016).
1754   209.   Jesky, M.D. et al. Health-Related Quality of Life Impacts Mortality but Not Progression to
1755   End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational
1756   Study. *PLoS One* **11**, e0165675 (2016).
1757   210.   Rebollo Rubio, A., Morales Asencio, J.M. & Eugenia Pons Raventos, M. Depression, anxiety
1758   and health-related quality of life amongst patients who are starting dialysis treatment. *J Ren
1759   Care* (2017).
1760   211.   Davison, S.N., Jhangri, G.S. & Johnson, J.A. Cross-sectional validity of a modified Edmonton
1761   symptom assessment system in dialysis patients: a simple assessment of symptom burden.
1762   *Kidney Int* **69**, 1621-5 (2006).
1763   212.   Davison, S.N. Pain in hemodialysis patients: prevalence, cause, severity, and management.
1764   *Am J Kidney Dis* **42**, 1239-47 (2003).
1765   213.   Pereira, B.D.S. et al. Beyond quality of life: a cross sectional study on the mental health of
1766   patients with chronic kidney disease undergoing dialysis and their caregivers. *Health Qual
1767   Life Outcomes* **15**, 74 (2017).
1768   214.   Tonelli, M. The roads less traveled? Diverging research and clinical priorities for dialysis
1769   patients and those with less severe CKD. *Am J Kidney Dis* **63**, 124-32 (2014).
1770   215.   Tinetti, M.E., Fried, T.R. & Boyd, C.M. Designing health care for the most common chronic
1771   condition--multimorbidity. *JAMA* **307**, 2493-4 (2012).
1772   216.   Cabrera, V.J., Hansson, J., Kliger, A.S. & Finkelstein, F.O. Symptom Management of the
1773   Patient with CKD: The Role of Dialysis. *Clin J Am Soc Nephrol* **12**, 687-693 (2017).
1774   217.   Manfredini, F. et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial.
1775   *J Am Soc Nephrol* **28**, 1259-1268 (2017).
1776   218.   Cameron, J.I., Whiteside, C., Katz, J. & Devins, G.M. Differences in quality of life across renal
1777   replacement therapies: a meta-analytic comparison. *Am J Kidney Dis* **35**, 629-37 (2000).
1778   219.   Iyasere, O.U. et al. Quality of Life and Physical Function in Older Patients on Dialysis: A
1779   Comparison of Assisted Peritoneal Dialysis with Hemodialysis. *Clin J Am Soc Nephrol* **11**, 423-
1780   30 (2016).
1781   220.   Vanholder, R. et al. Reducing the costs of chronic kidney disease while delivering quality
1782   health care: a call to action. *Nat Rev Nephrol* **13**, 393-409 (2017).
1783   221.   Dew, M.A. et al. Does transplantation produce quality of life benefits? A quantitative analysis
1784   of the literature. *Transplantation* **64**, 1261-73 (1997).
1785   222.   Rhee, C.M., Brunelli, S.M., Subramanian, L. & Tentori, F. Measuring patient experience in
1786   dialysis: a new paradigm of quality assessment. *J Nephrol* (2017).
1787   223.   Levin, A., Lancashire, W. & Fassett, R.G. Targets, trends, excesses, and deficiencies:
1788   refocusing clinical investigation to improve patient outcomes. *Kidney Int* **83**, 1001-9 (2013).
1789   224.   Wuttke, M. & Kottgen, A. Insights into kidney diseases from genome-wide association
1790   studies. *Nat Rev Nephrol* **12**, 549-62 (2016).

1791   225.   Beeman, S.C. et al. MRI-based glomerular morphology and pathology in whole human
1792   kidneys. *Am J Physiol Renal Physiol* **306**, F1381-90 (2014).

1793   226.   Boor, P., Ostendorf, T. & Floege, J. Renal fibrosis: novel insights into mechanisms and
1794   therapeutic targets. *Nat Rev Nephrol* **6**, 643-56 (2010).

1795   227.   Tampe, D. & Zeisberg, M. Potential approaches to reverse or repair renal fibrosis. *Nat Rev*
1796   *Nephrol* **10**, 226-37 (2014).

1797   228.   Voelker, J. et al. Anti-TGF-beta1 Antibody Therapy in Patients with Diabetic Nephropathy. *J*
1798   *Am Soc Nephrol* **28**, 953-962 (2017).

1799   229.   Goicoechea, M. et al. Allopurinol and progression of CKD and cardiovascular events: long-
1800   term follow-up of a randomized clinical trial. *Am J Kidney Dis* **65**, 543-9 (2015).

1801   230.   de Zeeuw, D. et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney
1802   disease. *N Engl J Med* **369**, 2492-503 (2013).

1803   231.   Pergola, P.E. et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N*
1804   *Engl J Med* **365**, 327-36 (2011).

1805   232.   Lazzeri, E., Romagnani, P. & Lasagni, L. Stem cell therapy for kidney disease. *Expert Opin Biol*
1806   *Ther* **15**, 1455-68 (2015).

1807   233.   Lasagni, L. et al. Podocyte Regeneration Driven by Renal Progenitors Determines Glomerular
1808   Disease Remission and Can Be Pharmacologically Enhanced. *Stem Cell Reports* **5**, 248-63
1809   (2015).

1810   234.   Mazzinghi, B., Romagnani, P. & Lazzeri, E. Biologic modulation in renal regeneration. *Expert*
1811   *Opin Biol Ther* **16**, 1403-1415 (2016).

1812   235.   Pichaiwong, W. et al. Reversibility of structural and functional damage in a model of
1813   advanced diabetic nephropathy. *J Am Soc Nephrol* **24**, 1088-102 (2013).

1814   236.   Cianciolo Cosentino, C. et al. Histone deacetylase inhibitor enhances recovery after AKI. *J Am*
1815   *Soc Nephrol* **24**, 943-53 (2013).

1816   237.   Klinkhammer, B.M., Goldschmeding, R., Floege, J. & Boor, P. Treatment of Renal Fibrosis-
1817   Turning Challenges into Opportunities. *Adv Chronic Kidney Dis* **24**, 117-129 (2017).

1818   238.   Kramann, R. et al. Pharmacological GLI2 inhibition prevents myofibroblast cell-cycle
1819   progression and reduces kidney fibrosis. *J Clin Invest* **125**, 2935-51 (2015).

1820   239.   Peired, A.J., Sisti, A. & Romagnani, P. Mesenchymal Stem Cell-Based Therapy for Kidney
1821   Disease: A Review of Clinical Evidence. *Stem Cells Int* **2016**, 4798639 (2016).

1822   240.   Ninichuk, V. et al. Multipotent mesenchymal stem cells reduce interstitial fibrosis but do not
1823   delay progression of chronic kidney disease in collagen4A3-deficient mice. *Kidney Int* **70**, 121-
1824   9 (2006).

1825   241.   Xinaris, C. et al. Functional Human Podocytes Generated in Organoids from Amniotic Fluid
1826   Stem Cells. *J Am Soc Nephrol* **27**, 1400-11 (2016).

1827   242.   Takasato, M. et al. Kidney organoids from human iPS cells contain multiple lineages and
1828   model human nephrogenesis. *Nature* **536**, 238 (2016).

1829   243.   Takasato, M. & Little, M.H. Making a Kidney Organoid Using the Directed Differentiation of
1830   Human Pluripotent Stem Cells. *Methods Mol Biol* **1597**, 195-206 (2017).

1831   244.   Xinaris, C., Brizi, V. & Remuzzi, G. Organoid Models and Applications in Biomedical Research.
1832   *Nephron* **130**, 191-9 (2015).

1833   245.   Anders, H.J., Jayne, D.R. & Rovin, B.H. Hurdles to the introduction of new therapies for
1834   immune-mediated kidney diseases. *Nat Rev Nephrol* **12**, 205-16 (2016).

1835   246.   Holderied, A. & Anders, H.J. Animal models of kidney inflammation in translational medicine.
1836   *Drug Discovery TOday: Disease Models* **11**, 19-27 (2014).

1837   247.   Jayne, D.R. et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated
1838   Vasculitis. *J Am Soc Nephrol* (2017).

1839   248.   Ketteler, M. et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and
1840   Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int*
1841   **92**, 26-36 (2017).

1842   249.   Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice
1843   Guideline for Lipid Management in Chronic Kidney Disease. *Kidney inter., Suppl.* **3**, 259–305
1844   (2013).
1845   250.   Farrington, K. et al. Clinical Practice Guideline on management of older patients with chronic
1846   kidney disease stage 3b or higher (eGFR<45 mL/min/1.73 m2): a summary document from the
1847   European Renal Best Practice Group. *Nephrol Dial Transplant* **32**, 9-16 (2017).
1848   251.   Klessens, C.Q. et al. An autopsy study suggests that diabetic nephropathy is underdiagnosed.
1849   *Kidney Int* **90**, 149-56 (2016).

1850

1851

1852   **References to highlight**

1853   **Introduction:**
1854
1855   Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline
1856   for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* **3**, 1-150 (2013).
1857   **Latest classification of CKD now implementing also albuminuria in a 2D matrix for stratification of the**
1858   **risk for CKD progression and complications.**
1859

1860

1861   **Epidemiology:**
1862   Bello, A.K. et al. Assessment of Global Kidney Health Care Status. *JAMA* **317**, 1864-1881 (2017).
1863   **Latest overview about kidney health care in all regions of the world displaying wide variation of**
1864   **access to nephrology specialists, quality of diagnostic workup, and preferences for kidney**
1865   **replacement therapy.**
1866
1867   Benghanem Gharbi, M. et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult
1868   population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD. *Kidney Int* **89**, 1363-71
1869   (2016).
1870   **CKD population study performed in Marocco presenting percentiles for repeated eGFR. Such GFR**
1871   **percentiles of the respective local population would be extremely useful for patient care.**
1872

1873

1874   **Pathophysiology**
1875

1876   Laouari, D. et al. TGF-alpha mediates genetic susceptibility to chronic kidney disease. *J Am Soc Nephrol*
1877   **22**, 327-35 (2011).
1878   **First description of the TGF-alpha/EGFR axis as a driver of compensatory growth of remnant**
1879   **nephrons. Targeting this pathway can limit the the adaptive response turning into a maladaptive**
1880   **pathomechanism of CKD progression.**
1881

1882   Peired, A. et al. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. *J Am Soc*
1883   *Nephrol* **24**, 1756-68 (2013).
1884   **Description of how proteinuria suppresses podocyte regeneration from local podocyte precursors**
1885   **inside the glomerulus.**
1886

1887   Beckerman, P. et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney
1888   disease in mice. *Nat Med* **23**, 429-438 (2017)
1889

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)

1942   **Improving quality of life starts with its proper assessment.**

1943

1944   Iyasere, O.U. et al. Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of

1945   Assisted Peritoneal Dialysis with Hemodialysis. *Clin J Am Soc Nephrol* **11**, 423-30 (2016).

1946   **Evaluating alternative options to hemodialysis for older ESKD patients.**

1947

1948

1949

1950   **Outlook**

1951

1952   Levin, A. et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research,

1953   and policy. *Lancet* (2017).

1954   **Roadmap on how to close gaps in global kidney health**

1955

1956

1957

1958

1959

1960

1961

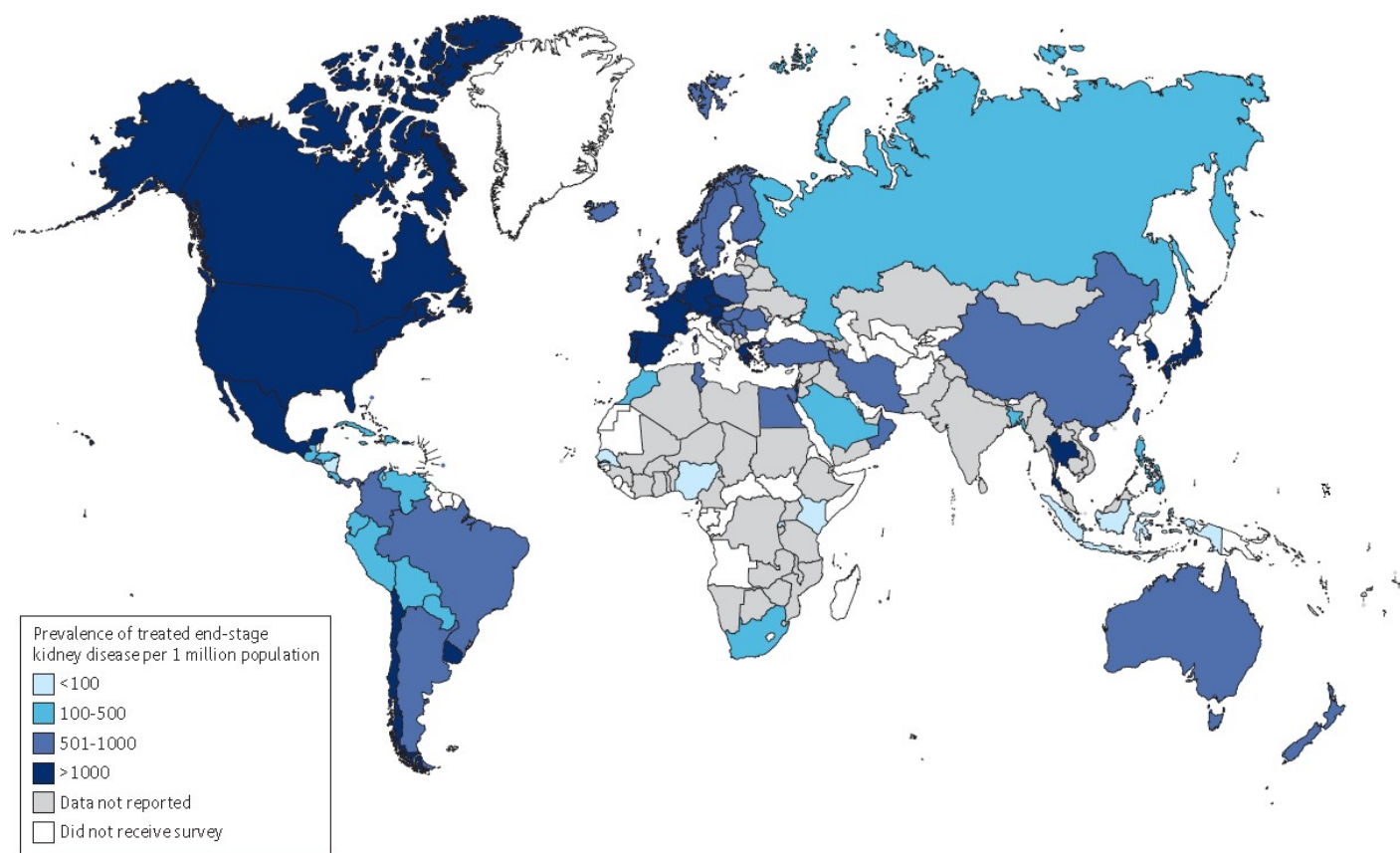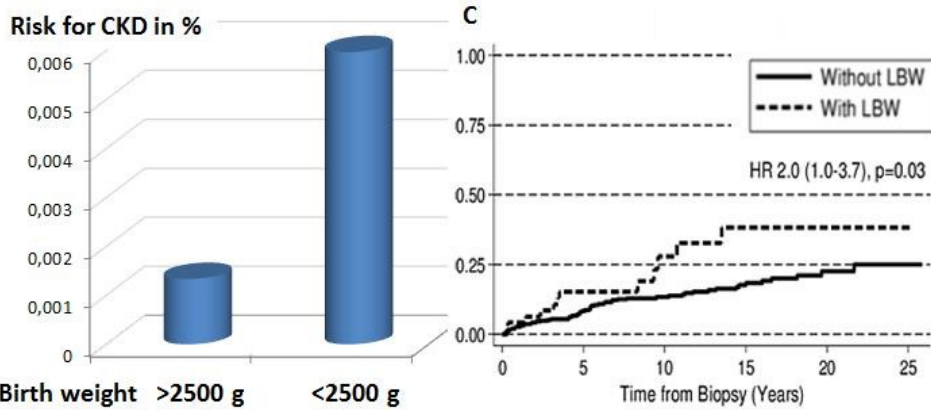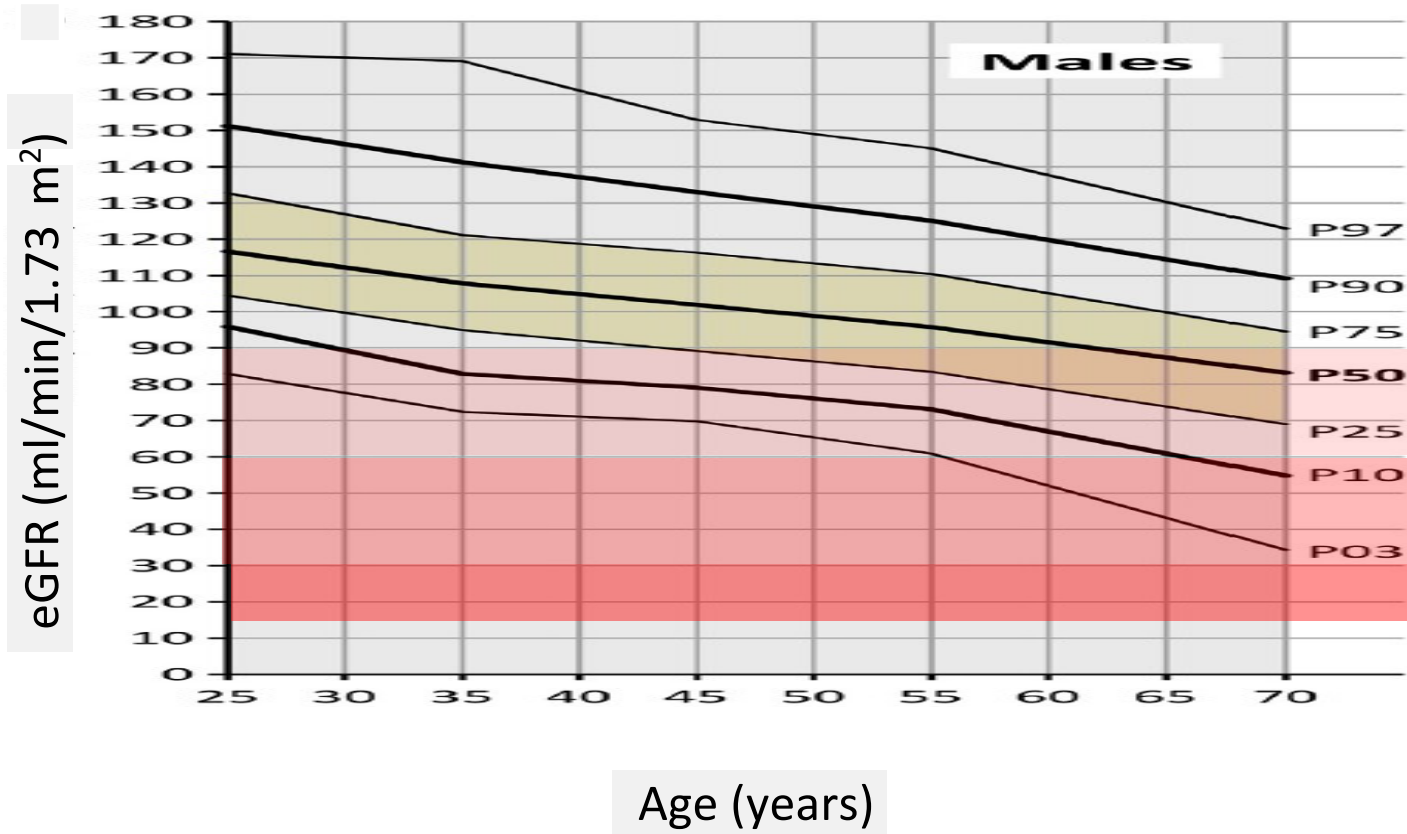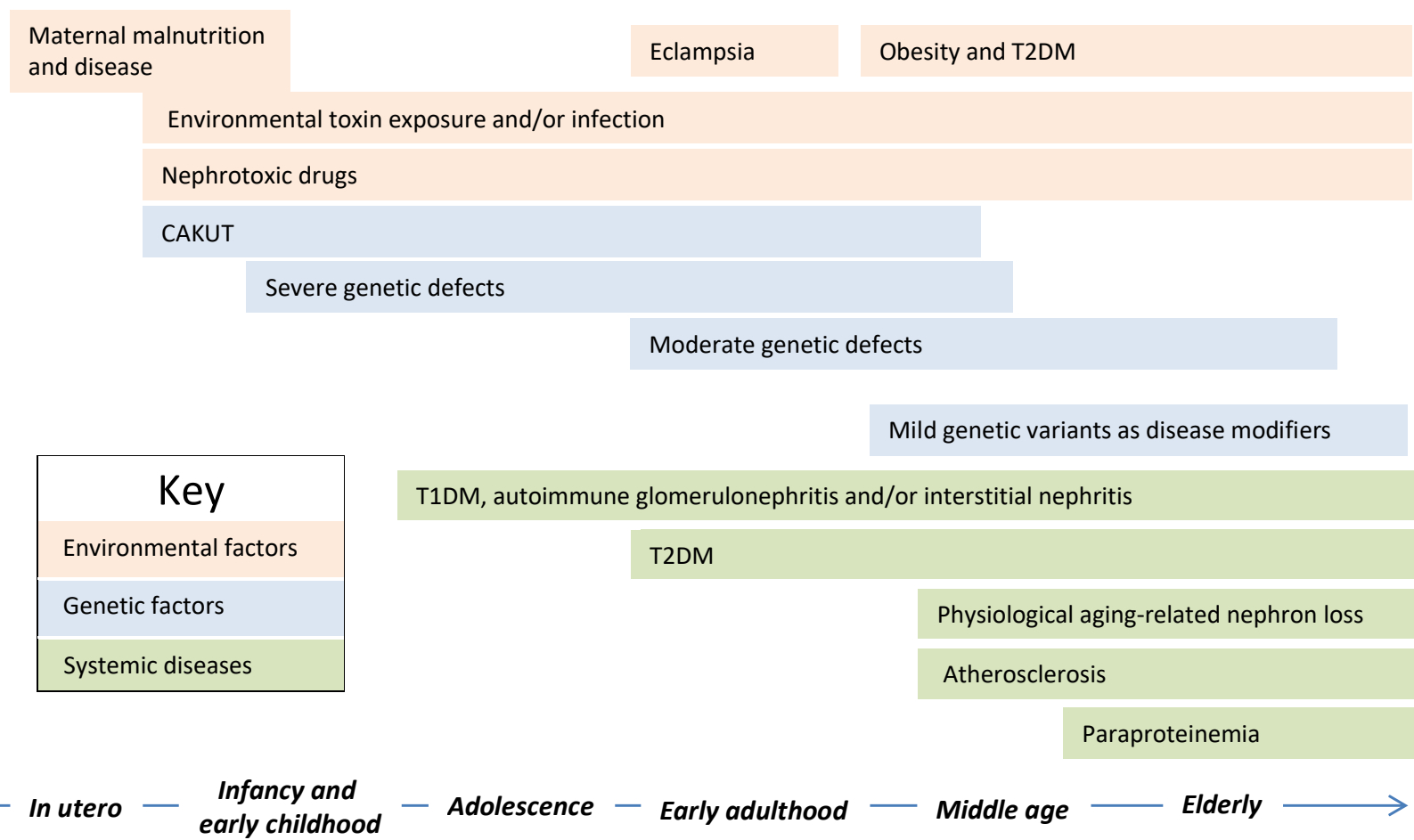1962

1963

1964

1965

1966

1967

1968

1969

1970

1971

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased <30 mg/g <3 mg/mmol	**A2** Moderately increased 30-300 mg/g 3-30 mg/mmol	**A3** Severely increased >300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m²) Description and range	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.

Prevalence of treated end-stage kidney disease per 1 million population

- <100
- 100-500
- 501-1000
- >1000
- Data not reported
- Did not receive survey

eGFR (ml/min/1.73 m²) vs Age (years) — Males

Risk for CKD in %

HR 2.0 (1.0-3.7), p=0.03

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

T1DM, autoimmune glomerulonephritis and/or interstitial nephritis

T2DM

Physiological aging-related nephron loss

Atherosclerosis

Paraproteinemia

Key

Environmental factors

Genetic factors

Systemic diseases

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

Excessive podocyte shear stress causing podocyte detachment

TGFα/EGFR

PEC-driven FSGS

Proteinuria

podocyte

PEC
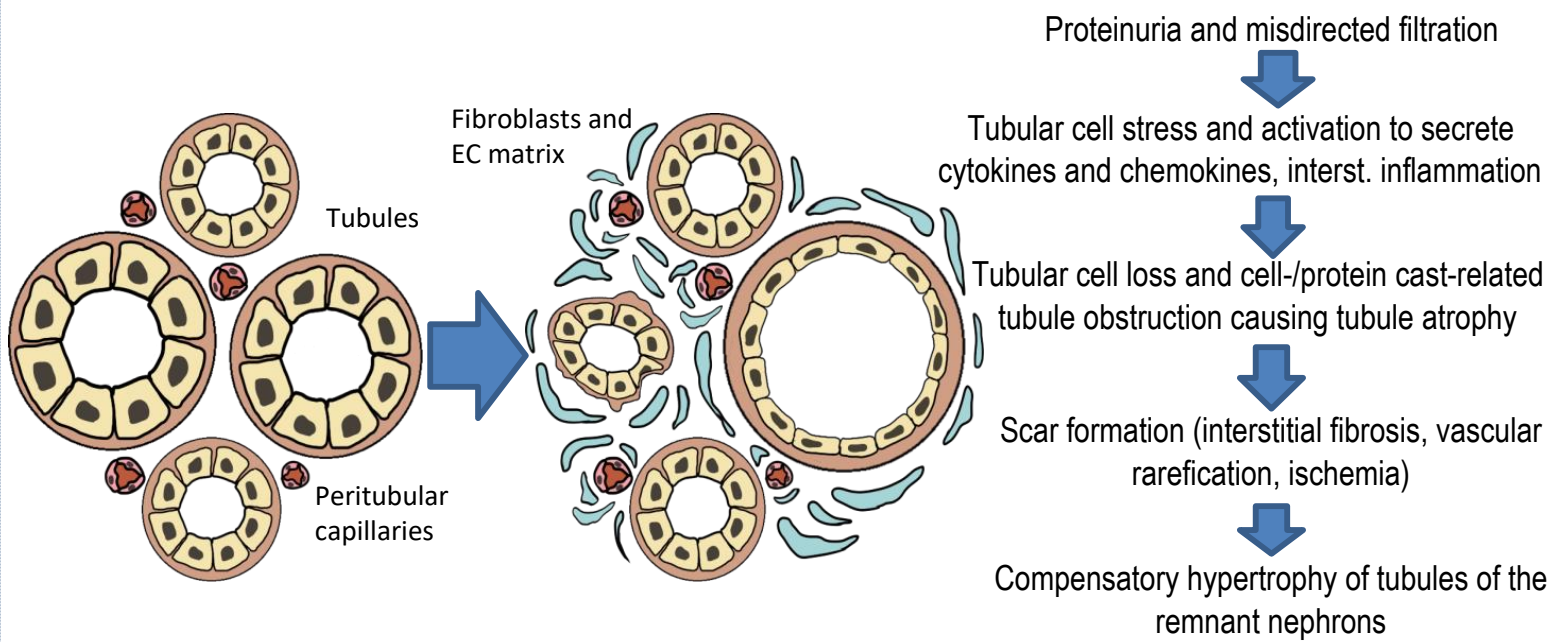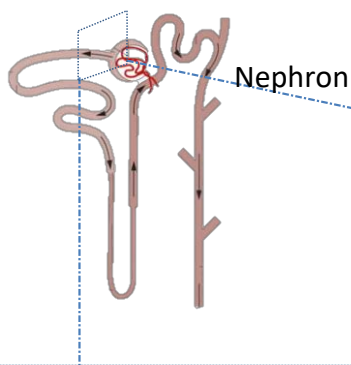
ECM

Detaching podocyte

Blood vessel

proteinuria

gure 5B

Nephron

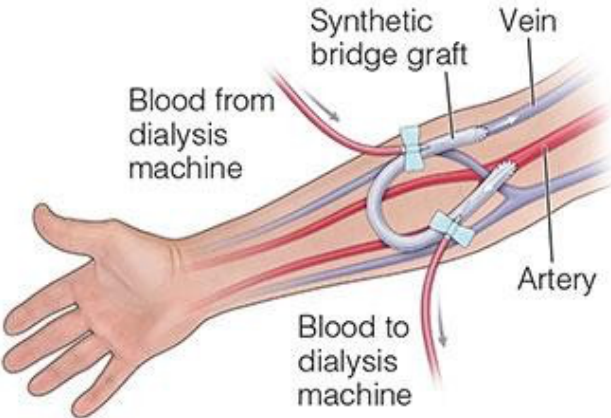Fibroblasts and
EC matrix

Tubules

Peritubular
capillaries

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

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

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

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

1.Enhancing podocyte regeneration

2. Enhancing tubular regeneration
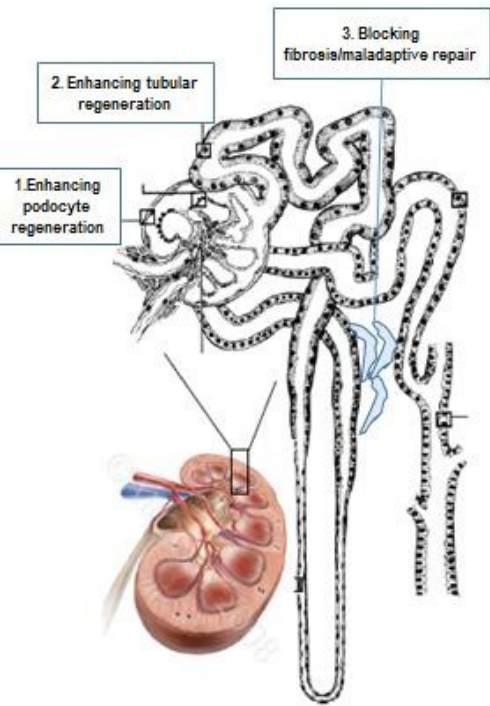
3. Blocking fibrosis/maladaptive repair

1A.Promoting PEC progenitor differentiation into podocytes:
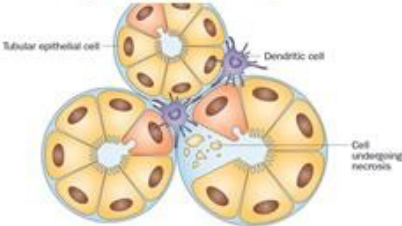
1B.Blocking PEC progenitor overgrowth and matrix production
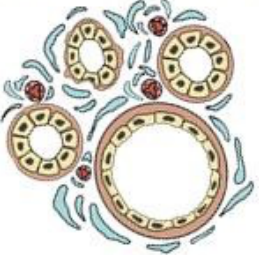
GSK3 inhibitors
Retinoic acid
miRNA 193a
RAS inhibitors
Leptin

SDF1 antagonists
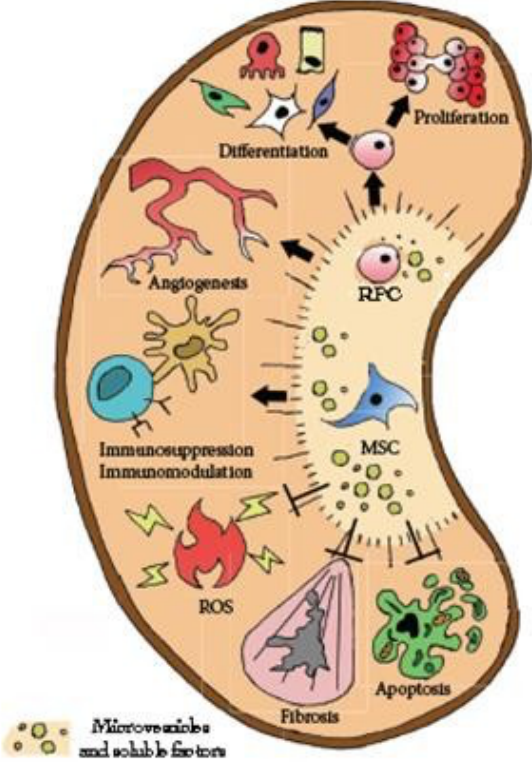Steroids/Steroid receptor inhibitors
Notch antagonists

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

A

Differentiation

Proliferation

Angiogenesis

RFC

Immunosuppression
Immunomodulation

MSC

ROS

Fibrosis

Apoptosis

Microvesicles
and soluble factors

B

iPSC, ESC

Cell monolayer

Early renal clusters

replated in
3D culture

Genetic editing

Kidney organoid

Functional testing,
Disease modeling