Web Appendix files – Manuscript: THELANCET-D-16-07352, Global Kidney Health 2017 and beyond: A roadmap for closing gaps in care, research, and policy

Figure 1 CKD prevalence illustrated using KDIGO's eGFR / albuminuria grid[1] (adaptation of data from Hill et al.)[2]

			Albuminuria Categories (mg/g creatinine)		
			A1	**A2**	**A3**
			< 30	30-300	> 300
GFR Categories (mL/min x 1.73 m^2)	G1	≥ 90		3.5 (2.8-4.2) %	
	G2	60-89		3.9 (2.7-5.3) %	
	G3a	45-59	7.6 (6.4-8.9) %		
	G3b	30-44			
	G4	15-29	0.4 (0.3-0.5) %		
	G5	< 15	0.1 (0.1-0.1) %		

Figure 2 Heatmap of risk of AKI as a function of pre-existing eGFR and albuminuria in diabetics and non-diabetics[3]

eGFR	No Diabetes ACR/Dipstick <10 / "–"	10-29 / "±"	30-299 / "1+"	300+ / "≥2+"		Diabetes ACR/Dipstick <10 / "–"	10-29 / "±"	30-299 / "1+"	300+ / "≥2+"	
≥105	1.01 (0.59-1.70)	1.89 (0.86-4.16)	**3.05** (1.37-6.78)	**9.32** (4.20-20.67)	0.82 (0.48-1.41)	1.14 (0.57-2.27)	1.81 (0.96-3.42)	**3.04** (1.19-7.78)	**9.39** (4.16-21.21)	1.17 (0.66-2.08)
90-104	0.93 (0.73-1.18)	1.36 (0.75-2.47)	**2.83** (2.13-3.78)	**6.59** (3.31-13.13)	0.90 (0.68-1.20)	0.82 (0.63-1.07)	**1.32** (1.00-1.73)	**2.40** (1.52-3.79)	**5.50** (4.19-7.22)	0.85 (0.61-1.20)
75-89	1.00 (reference)	**1.97** (1.66-2.34)	**3.51** (2.68-4.60)	**6.74** (5.30-8.58)	1.00 (reference)	1.00 (reference)	**1.70** (1.18-2.44)	**2.49*** (2.11-2.93)	**4.73*** (3.14-7.12)	1.00 (reference)
60-74	**1.66** (1.53-1.80)	**2.84** (2.04-3.95)	**4.48** (3.50-5.73)	**8.56** (6.75-10.86)	**1.60** (1.47-1.73)	**1.36*** (1.20-1.53)	**2.12*** (1.80-2.49)	**3.54*** (2.72-4.60)	**6.82*** (5.79-8.05)	**1.41*** (1.30-1.53)
45-59	**3.06** (2.41-3.89)	**5.48** (3.82-7.86)	**7.41** (5.56-9.87)	**14.08** (11.16-17.75)	**2.72** (2.22-3.34)	**2.89*** (2.05-4.09)	**3.24*** (2.15-4.89)	**4.70*** (3.05-7.24)	**8.75*** (5.87-13.05)	**2.10*** (1.63-2.71)
30-44	**7.87** (6.03-10.28)	**9.18** (6.05-13.94)	**14.29** (9.25-22.10)	**24.91** (15.31-40.54)	**5.83** (4.63-7.36)	**5.27*** (3.86-7.20)	**6.30*** (4.16-9.54)	**9.08*** (7.83-10.54)	**15.62*** (10.51-23.23)	**3.96*** (3.41-4.60)
15-29	**19.36** (16.91-22.18)	**25.69** (13.20-49.99)	**28.46** (23.74-34.10)	**39.18** (29.32-52.36)	**10.68** (8.05-14.17)	**9.80*** (7.25-13.23)	**17.27*** (8.34-35.79)	**15.91*** (12.30-20.58)	**23.53*** (16.08-34.44)	**6.68*** (5.57-8.03)
	1.00 (reference)	**1.59** (1.32-1.93)	**2.58** (2.30-2.90)	**4.00** (3.16-5.06)		1.00 (reference)	**1.46** (1.25-1.70)	**2.08*** (1.95-2.22)	**3.44** (2.78-4.24)	

Figure 3 Number of associated genes/loci for monogenic and complex kidney diseases and their overlap (adaptation of figure from Wuttke)[4]

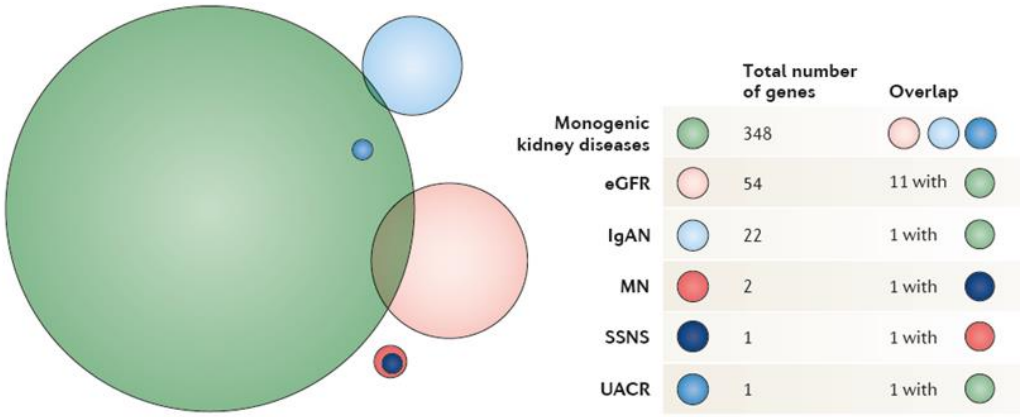

Figure 3 | **Overlap of GWAS and monogenic kidney disease genes.** Certain monogenic kidney disease genes map into loci identified by genome-wide association studies (GWAS) of the chronic kidney disease (CKD)-defining traits estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR), or identified by GWAS of certain CKD aetiologies such as IgA nephropathy (IgAN). This pattern of overlap might be indicative of a continuum between rare disruptive mutations and common regulatory variants in genes that are important for kidney development and function. Note that GWAS of CKD (determined as eGFR<60 ml/min/1.73 m^2) in population-based settings has led to the identification of five loci, all of which have also been found in GWAS of eGFR. MN, membranous nephropathy; SSNS, steroid-sensitive nephrotic syndrome.

Target	Therapy	Status/Results	Trial Registration #
Diabetic Nephropathy	Aliskiren (ALTITUDE)	Phase 3 study terminated due to harm[5]	NCT00549757
	Anti-connective tissue growth factor (CTGF) antibody FG-3019	Phase 2 study terminated due to suboptimal design	NCT00913393
	Anti-transforming growth factor-beta (TGF-β) kinase antibody (LY2382770)	Phase 2 study terminated due to lack of efficacy	NCT01113801
	Bardoxolone Methyl	Phase 3 study terminated due to safety concerns	NCT01351675
	C-C chemokine receptor type 2 (CCR2) antagonism	Phase 2 study completed[6]	NCT01447147
	Endothelin-A antagonist Atrasentan	Phase 3 study currently recruiting	NCT01858532
	Mineralocorticoid antagonist	Phase 2 study completed[7]	NCT01874431
	Nox1/4 inhibitor (Oral GKT137831)	Phase 2 study completed: negative results	NCT02010242
	Phosphodiesterase 5 inhibitor	Phase 2 study completed[8]	NCT01200394
	Pirfenidone	Phase 1, 2 study completed: results not reported	NCT02408744
	Pyridorin	Phase 3 study terminated due to lack of funding	NCT02156843

Target	Therapy	Status/Results	Trial Registration #
IgA Nephropathy	Blisibimod	Phase 2, 3 study active but not recruiting	NCT02062684
	Bortezomib	Phase 4 study recruiting	NCT01103778
	Combination immuosuppression (STOP IgA)	Phase 3 study completed: negative results and a signal for harm[9]	NCT00554502
	Fostamatinib	Phase 2 study recruiting	NCT02112838
	Nefecon	Phase 2 study completed: reported positive outcomes	NCT01738035
	Rituximab	Phase 4 study recruiting	NCT02571842
	Rituximab	Phase 4 study completed	NCT00498368
	Steroids in IgA nephropathy (TESTING)	Study active but not recruiting, modified due to harm signal	NCT01560052
Proteinuric CKD	Curcumin	Phase 3 study completed: results not reported	NCT01831193
	LCZ696 (UK HARP-III)	Study active but not recruiting	ISRCTN11958993
Adult PKD	Octreotide LAR (ALADIN 2)	Phase 3 study active but not recruiting	NCT01377246
	Octreotide LAR (ALADIN)	Phase 3 study competed[10]	NCT00309283
	Sirolimus	Phase 2,3 study terminated due to safety and efficacy concerns[11]	NCT01223755
	Tolvaptan	Phase 3 study active but not recruiting in patients with CKD Stage 2-4	NCT02160145
	Tolvaptan (TEMPO 3/4)	Phase 3 study completed[12,13]	NCT00428948
	Water loading	Observational study completed: results not yet reported	NCT01348035
Lupus Nephritis	Abatacept	Phase 2 study completed: negative results[14]	NCT00774852
		Phase 3 study active but not recruiting	NCT01714817
	Atacicept	Phase 2, 3 study terminated due to safety issues	NCT00573157
	Belimumab	Phase 3 study recruiting	NCT01639339
	Blisibimod	Phase 3 study recruiting	NCT02514967
	Etanercept	Phase 2 study terminated: perceived risk-benefit ratio for individuals with early active RA	NCT00447265
	Infliximab	Phase 2,3 study terminated due to failure to recruit	NCT00368264
	Rituximab	Phase 3 study completed: negative results[15]	NCT00282347
		Phase 3 study recruiting (as a single agent + standard of care)	NCT01673295
		Phase 2 study recruiting (in combination with Belimumab)	NCT02260934
		Phase 3 study recruiting (in combination with Mycophenolate Mofetil)	NCT01773616

Target	Therapy	Status/Results	Trial Registration #
Anti-Neutrophil Cytoplasmic Antibody (ANCA) vasculitis	Alemtuzumab	Phase 4 study, status unknown	NCT01405807
	Eculizumab	Phase 2 study terminated due to failure of patient enrolment	NCT01275287
Miscellaneous	Eculizumab in C3 GN and dense deposit disease	Phase 1 study, status unknown	NCT01221181
	Rituximab in relapsing idiopathic nephrotic syndrome	Phase 3 study completed[16]	NCT00981838

Table 1 Recent Therapeutic Trials for CKD

Figure 4 Timeline of translation from SNP discovery to clinical application (adaptation of figure from Fox).[17] Translation of genetic findings from their discovery to insights into the underlying molecular mechanisms and to clinical application can take decades and is associated with high costs

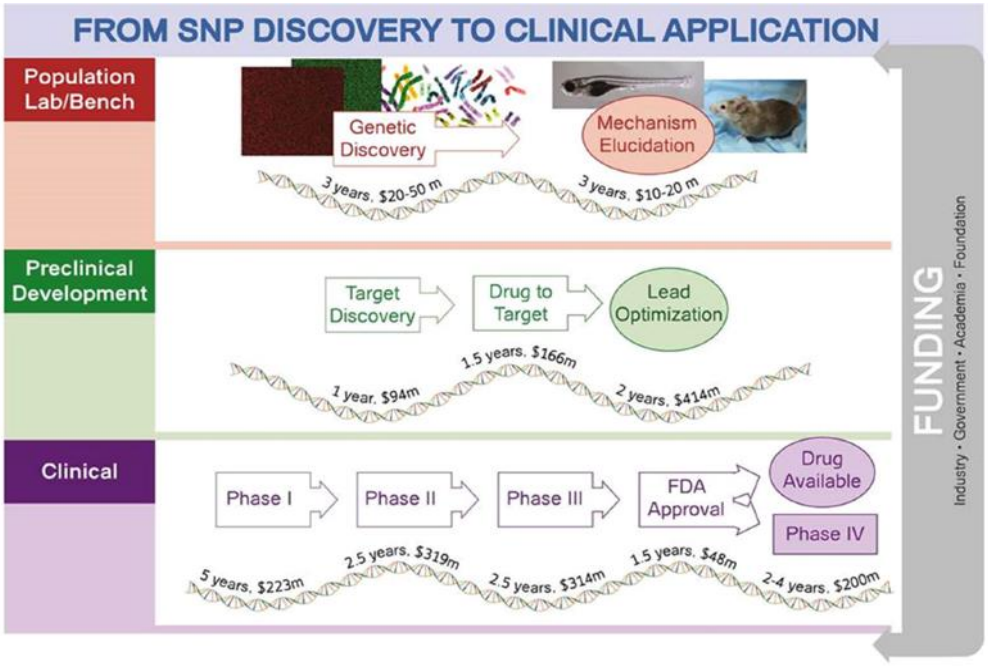

Figure 2. Steps, timeline, and approximate costs for the key steps from single-nucleotide polymorphism (SNP) identification to achieving clinical utility. Timeline and costs based on Paul et al.[91] The figure should be read from left to right, starting at the top. Please note that the timeline reflects the current pace of drug development. We acknowledge the National Human Genome Research Institute Digital Media Database for the elements in this schematic (http://www.genome.gov/dmd/). FDA indicates US Food and Drug Administration.

Figure 5 Geospatial risk analysis for IgA nephropathy (figure from Kiryluk)[18] based on the distribution of a standardized genetic risk score from populations sampled around the World

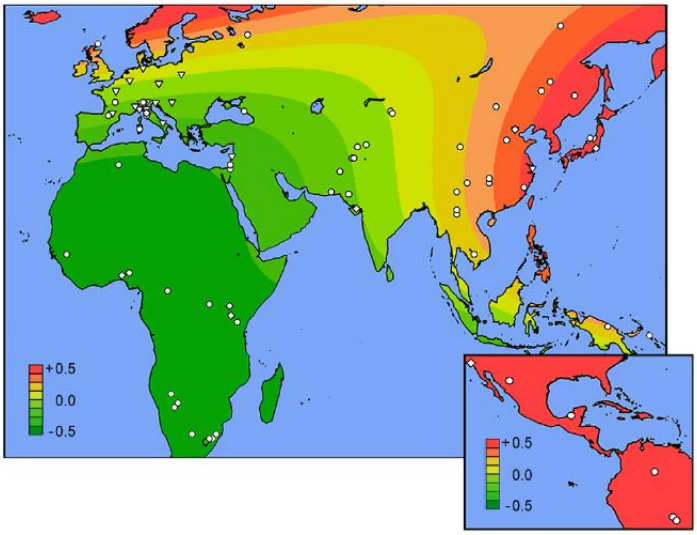

Figure 3. Worldwide geospatial risk analysis. Surface interpolation of the standardized risk score over Africa and Euroasia (main), and Americas (inset). Symbols represent the locations of sampled populations: HGDP (circles), HapMap-III (diamonds), and healthy controls from this study (triangles).

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