



# The Use of Genomics To Drive Kidney Disease Drug Discovery and Development

Dermot F. Reilly  and Matthew D. Breyer 

## Abstract

As opposed to diseases such as cancer, autoimmune disease, and diabetes, identifying drugs to treat CKD has proven significantly more challenging. Over the past two decades, new potential therapeutic targets have been identified as genetically altered proteins involved in rare monogenetic kidney diseases. Other possible target genes have been implicated through common genetic polymorphisms associated with CKD in the general population. Significant challenges remain before translating these genetic insights into clinical therapies for CKD. This paper will discuss how genetic variants may be leveraged to develop drugs and will especially focus on those genes associated with CKD to exemplify the value and challenges in including genetic information in the drug development pipeline.

CJASN 15: ●●●–●●●, 2020. doi: <https://doi.org/10.2215/CJN.11070919>

## Introduction

Accelerating the delivery of therapies to patients with kidney disease has proven a significant challenge. Research and development costs for drug development continue to increase; they are now estimated to range from US\$3 to 12 billion per successful launch (1,2). These enormous costs are in large part due to our fundamental lack of understanding of the human biology underpinning disease and the incomplete translatability of preclinical animal studies to people. Human genetic information offers the promise to bridge this gap by providing evidence that a gene is directly involved in human disease and is therefore a valid drug target. Target validation typically follows the initial nomination of a protein or molecule as a potential drug target and involves experiments that aim to confirm a hypothesis that perturbation of the drug target will result in therapeutic benefit with minimal adverse effects (Figure 1). Although preclinical models are a critical component of target validation, the availability of supporting data for a mechanism in humans, especially in a relevant patient population of interest, is highly desirable and substantially enriches the odds of success (3). The evolution of genetics and genomics and its application to human disease cohorts collected over recent decades has provided new opportunities for drug discovery, implicating unexpected gene targets involved in human disease mechanisms at an earlier point in the drug development process (4). In many cases, human genetics offers information on direct perturbation of a target gene with directional insight on the functional effects with respect to both potential benefit and safety concerns. Genetic studies can provide insights on the consequences of perturbation of therapeutic mechanisms over time and provide a means to understand the pleiotropic effects of target mechanisms on phenotypic traits in advance of clinical development. This review will focus on the utility of genetics in drug discovery and development

in more common complex forms of CKD, including diabetic kidney disease and IgA nephropathy. We will discuss approaches that have delivered clinically successful drugs and touch only briefly on newer aspirational approaches including genome wide CRISPR/Cas manipulation and induced pluripotent stem cell-derived organoids.

## Genetics Contributions to Drug Discovery in Metabolic Disease

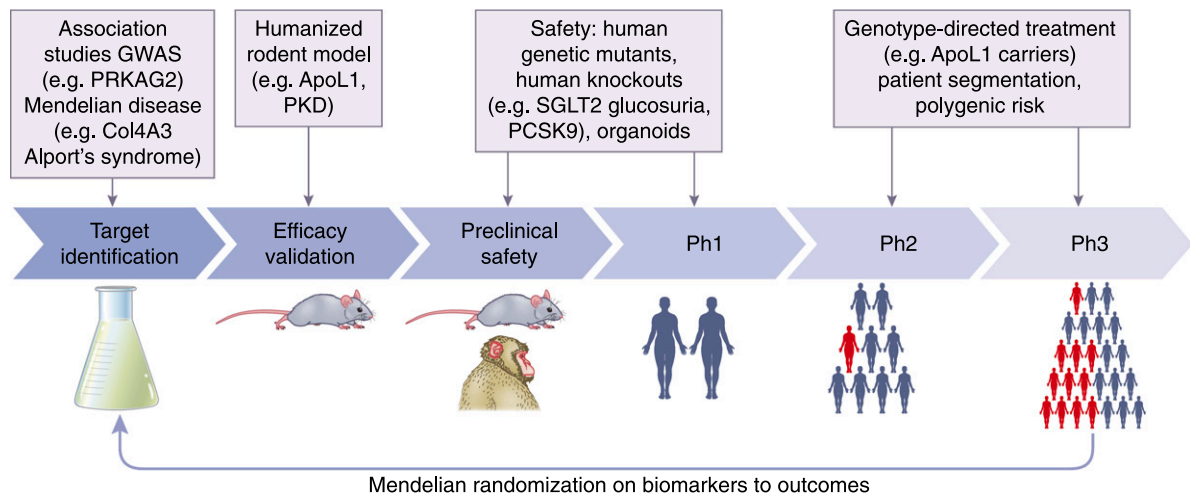
Human genetic and mRNA expression data have helped identify novel targets that have informed drug discovery and development for diverse diseases, particularly in cell autonomous disorders like cancer (5–7). Genetics has also significantly contributed to our understanding of metabolic diseases especially for drug development in disorders of cholesterol and triglyceride metabolism leading to atherosclerotic cardiovascular risk (4,8,9). Nevertheless, the discovery of drugs to prevent the progression of kidney disease has proven painfully slow with only two beneficial classes of drugs identified: angiotensin pathway inhibitors and the recent addition of SGLT2 inhibition for diabetic kidney disease.

In the field of cholesterol and lipid biology, insights from human genetics contributed to an improved understanding of causal links between LDL cholesterol and heart disease. The story of how coding variation in PCSK9 inspired antibody-based therapeutics and subsequent therapeutic modalities in clinical development has been well described (4,10). In the case of HDL cholesterol, observational epidemiology had established a relationship of HDL with protection from coronary diseases, but human genetic studies of a common coding variant in endothelial lipase brought the lack of a clear causal relationship between HDL and coronary disease to the fore (11). 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase, the target of

Cardiovascular and Metabolism Discovery Research, Janssen Research and Development LLC, Boston, Massachusetts

## Correspondence:

Dr. Matthew D. Breyer, Cardiovascular and Metabolism Discovery Research, Janssen Research and Development LLC, 4 Blackfan Circle, Boston, MA 02115. Email: [mbreyer@its.jnj.com](mailto:mbreyer@its.jnj.com)



**Figure 1. | The use of genetic information in drug development.** The blue arrows depict the multiple stages of drug development from preclinical testing to validation in large clinical studies. Development of a drug to treat kidney disease begins with target identification and generation of a molecule that affects activity of the target. A gene involved in human kidney disease may themselves present a drug target or at least validate pathways involved in human disease. Once pharmacologic tools have been generated to the target, their activity is often validated in animal models of the disease as a means to de-risk extremely costly clinical trials. Genetic diseases may also inform extrarenal consequences of the genetic disruption and thereby de-risk safety concerns. Once safety has been established, genetics might be used to segment disease populations into those subjects who may derive greater benefit from the drug. Finally, patients carrying polymorphisms for genes may themselves be studied to validate involvement of altered gene activity in progression of a disease through Mendelian randomization and further inform target identification or validation. GWAS, genome-wide association study; Ph1/2/3, phase 1/2/3; PKD, polycystic kidney disease.

statin medications, is supported by genome-wide association studies (GWAS) data that emerged after the development of the drugs, but the small effect sizes of these alleles were capable of replicating clinical observation of incident diabetic risk associated with lowering of LDL cholesterol (12). Thus, insight relating to efficacy and safety for putative kidney disease therapeutics may similarly lie within the association data for kidney disease and kidney function (13).

Certainly, the exploration of genomic sequence has been essential for elucidating the basis of monogenic diseases like cystic fibrosis and polycystic kidney disease; however, successful application of these genetic insights toward drug development for kidney disease has not proven straightforward. Several recent publications have dealt with monogenic kidney diseases, including polycystic kidney disease (14), FSGS (15,16), and Alport disease (17). The ability to sequence the coding exome (see Table 1) of patients with kidney diseases of unclear etiology may also help inform the cause of kidney disease and thereby the clinical approach to treatment (18).

### Monogenic Disease Informs Drug Discovery

Cystic fibrosis represents a prototypic example of genetics advancing drug discovery in rare disease. It had long been recognized that patients with cystic fibrosis exhibit elevated sweat chloride concentration and cellular chloride permeability (19,20). The identification of the p.Phe508del in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in 1989 advanced the understanding that CFTR plays a role in ion transport regulation (21). Key insights were derived from the study of CFTR coding variants, including correlation of chloride channel dysfunction with cellular manifestations and clinical features, provision

of a tool enabling cystic fibrosis diagnosis, and connecting CFTR dysfunction with other observed phenotypes. Substantial progress has recently been achieved with small-molecule therapy for select disease-causing variants (22). It is sobering to consider that despite existing understanding of the functional ion transport defect this translation took >30 years from cloning of the CFTR gene to delivery of a clinical therapy.

### TRPC6 Mutations

Drug targets inspired by human monogenic kidney diseases are less advanced than cystic fibrosis. Current CKD standard-of-care medications have emerged from the traditional physiologic understanding of therapeutic mechanisms, rodent and human physiology and pharmacology. Nevertheless, the identification of dominant activating mutations in TRPC6 in familial FSGS (23,24) and expression in podocytes has inspired studies exploring the role of this target in hypertensive and diabetic kidney diseases (25,26). Study of TRPC5 inhibitors, a channel with a function similar to TRPC6 and also expressed in podocytes, were inspired by these studies and showed protective effects of this small molecule inhibitor in a rat model of hypertensive kidney disease (27). TRPC5/6 has attracted the interest of several large pharmaceutical companies for further exploration and development to treat FSGS and nephrotic syndrome, as well as its possible applicability to diabetic kidney disease and hypertensive kidney disease.

### SGLT2 Mutations

Identification of humans with familial isolated glucosuria provided an important foundation for studying its mechanistic basis defect, leading to identification of the glucose

**Table 1. Definitions of some commonly used terms**

Term	Definition
Complex diseases	Common multifactorial human disorders caused by a combination of genetic, environmental, and lifestyle factors, many of which are not yet identified.
Exome	The exome is composed of all of the exons within the genome, the sequences which, when transcribed, remain within the mature RNA after introns are removed by RNA splicing. This includes untranslated regions of mRNA and, importantly, the protein coding sequence.
GWAS	A now-fundamental approach to analyze genetic sequence variation throughout the genome that correlates alleles to different diseases and traits.
iPS	Cells derived from skin or blood that are reprogrammed back into an embryonic-like pluripotent state before subsequent development toward a desired human cell type.
Mendelian disease	Diseases (typically rare) caused by mutations in a single gene that sometimes run in families. Pedigree analyses of large families can determine disease-associated genes on autosomes or on a sex chromosome, and whether the related disease phenotype is dominant (involve damage to only one gene copy) or recessive (involving both gene copies).
Penetrance	The proportion of individuals carrying a particular variant of a gene that also express an associated trait. In medical genetics, the penetrance of a disease-causing mutation is the proportion of individuals with the mutation who exhibit clinical symptoms.
Pleiotropic Polymorphism	Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. A genetic variant within a population, upon which natural selection can operate.
PCSK9	An enzyme encoded on chromosome 1 that is causally linked to LDL cholesterol and has emerged as a prototypic genetic target
RNAi	Biologic process in which RNA molecules interfere and inhibit gene expression or translation by neutralizing targeted mRNA molecules
UMOD	Also known as Tamm–Horsfall protein, UMOD is a large glycoprotein normally found only in the ascending limb of the loop of Henle extending into the very early portion of the distal tubule. It is a major protein of normal urine and is the primary component of waxy nephron casts.

GWAS, genome-wide association study; iPS, induced pluripotent stem cells; PCSK9, proprotein convertase subtilisin/klexin type 9; RNAi, RNA interference; UMOD, uromodulin.

transporter SGLT2 (SLC5A2) (28). In 1947, Marble *et al.* (29) defined diagnostic criteria for the condition which was originally thought to be autosomal recessive. Kidney titration studies later characterized kidney glucosurias into type A and type B (30) and type O for individuals with a complete absence of glucose transport (31). The vast majority of the 44 mutations identified to date in the SLC5A2 gene that are associated with kidney glucosuria appear to be private, with a range of missense, nonsense, insertion/deletion, and splicing defects implicated. A splice mutant allele IVS7+5G has been observed in several unrelated families with familial kidney glucosuria from different ethnic backgrounds (32,33). Type A and B may be heterozygous, whereas patients with type O were determined to have homozygous or compound heterozygous disruption of the SGLT2 protein (32,34). It is important that patients with kidney glucosuria are not typically affected by severe clinical sequelae (33) because this helps inform the potential clinical safety of drugs targeting SGLT2—a major hurdle for drug development. In this case, however, genetics did not predict the profound therapeutic benefit of canagliflozin in diabetic kidney disease (35). Leveraging the understanding of kidney glucose transport was significantly enabled by the availability of the natural product phlorizin which was also known to inhibit kidney glucose absorption and served as a tool compound to enable development of SGLT2-selective pharmacologics (36). The low frequency of these identified private genetic variants did not enable advanced prediction of the cardio- and kidney-protective effects of inhibiting SGLT2 that was subsequently elucidated by clinical trials of the various marketed SGLT2-inhibiting agents (35,37–39).

Substantial challenges exist in translating genomic discoveries to approved medicines. Human genetics relies on the accumulation of informative alleles in target genes and their propagation through generations. When present, causal alleles represent a natural perturbation of a potential therapeutic target, but this perturbation may result from effects in noncoding regions with unclear interpretation. Although human genetics can help us gain additional insight on cause and effect, the mechanistic implications of a disease-associated genetic locus can be quite unclear when biologic characterization of the candidate causal gene is lacking.

### Common Genetic Variants and CKD

Initially GWAS offered great hope that they would provide a trove of new drug targets to treat disease (40,41). However, despite >200 gene polymorphisms associated with CKD being identified by GWAS of >1 million people (13), most implicated genes either do not appear readily “druggable” or their link to the pathogenesis of CKD remains unclear. These challenges are exemplified by the strongest CKD/diabetic kidney disease-associated polymorphisms near uromodulin (UMOD; also known as Tamm–Horsfall protein) (13,42,43). Although the Tamm–Horsfall protein was identified as the major protein normally excreted in human urine nearly 70 years ago (44), its physiologic function and role in the pathogenesis of CKD progression remains unclear. UMOD is an 85-kD, 616-amino acid, GPI-linked, membrane-associated glycoprotein (45) that is exclusively expressed in the kidney where its expression is restricted to the thick ascending limb and distal convoluted tubule. These nucleotide polymorphisms

do not affect UMOD amino acid sequence but are intergenic between UMOD and PDILT genes (43,46). The G risk allele at rs12917707 associates with increased urinary UMOD levels (47); however, whether altered UMOD excretion is a protective response, is itself pathogenic, or neither remains unclear. UMOD has been suggested to serve an anti-inflammatory role (48), however it may also serve as a chaperone for thick ascending limb membrane proteins contributing to increased sodium absorption and hypertension (49). Despite the seven decades of work on Tamm–Horsfall protein, neither the cellular target nor the downstream effectors of UMOD action have been definitively identified. Biologic targeting using UMOD itself as a therapeutic would be complicated by its large size and requirement of proper folding and maintenance of 24 cysteine-cysteine disulfide bonds (50). Similar experiences complicate targeting genetic variants associated with type 2 diabetes mellitus and Alzheimer disease GWAS in which TCF7L2 (51,52) and ApoE4 (53) polymorphisms respectively strongly associate, yet the biologic mechanisms underlying their genetic association with disease remains frustratingly obscure.

It is also notable that substantial differences in GWAS-identified risk alleles exist for kidney disease in type 1 diabetes mellitus versus type 2 diabetes mellitus. In a GWAS meta-analysis of 19,406 individuals with type 1 diabetes mellitus (54) both UMOD and PRKAG2 disease association polymorphisms replicated from larger CKD GWAS studies, but other single nucleotide polymorphisms did not achieve significance. Notably, the type 1 diabetes mellitus studies identified a significant protective coding polymorphism in collagen 4A3, a major component of the glomerular basement membrane. The strict inclusion of patients with type 1 diabetes mellitus represents an important distinction between these studies and GWAS studies associated with diabetic kidney disease in patients with type 2 diabetes mellitus, because kidney disease etiology in type 2 diabetes mellitus exhibits substantial heterogeneity with approximately 50% of subjects with type 2 diabetes mellitus exhibiting nondiabetic kidney disease (55). Subjects with type 1 diabetes mellitus kidney disease are younger (typically <50 years old) and likely represent more a homogeneous population of kidney disease etiology. These studies may be more representative of patients with pure diabetic kidney disease on biopsy than studies of patients with type 2 diabetes mellitus.

Other genes encoding membrane transporters primarily expressed in the proximal tubule have been identified in GWAS of both chronic nondiabetic and diabetic kidney disease and may prove tractable as pharmacologic targets (13,56). This possibility is underscored by the recent success of SGLT2 (SLC5A2) inhibition in the prevention of diabetic kidney disease progression (37,57). The mRNA expression of many of these CKD-associated transporters including SLC22A2 (OCT2, rs316019), SLC47A1 (MATE1, rs111653425), and SLC34A1 (NaPi2a, rs3812036) (58,59) is either enriched in or completely restricted to kidney. Similarly, monogenic disease in these genes can inform the safety of novel drugs targeting these transporters; however, in contrast to glucose transport where phlorizin provided a valuable tool compound for designing SGLT2 inhibitors, similar pharmacologic tools are lacking for many of these transporters.

It is perhaps surprising that polymorphisms in SGLT2 or other current validated therapeutic targets including angiotensin-converting enzyme (ACE), angiotensin receptor blocker, renin, and the mineralocorticoid receptor do not emerge as major signals in GWAS. In the years before genome-wide genotyping was enabled by the Hapmap Project and the Human Genome Project, candidate gene studies were typically performed on genes such as those of the renin-angiotensin-aldosterone system where biologic function was well understood. Although many of these candidate gene studies failed to replicate (60), the ACE insertion/deletion variant (rs1799752), which results in higher levels of circulating ACE enzyme activity, did associate with microalbuminuria and diabetic nephropathy in type 1 diabetes mellitus in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (61). As the sample sizes of GWAS studies have grown, genome-wide significant signals of association have been observed at the ACE gene locus with diastolic BP (62) and ACE activity (63). The modest effect size of these mutations is typical of GWAS; however, despite the established variability in BP as a trait, signals for other known hypertension drug targets, including CACNA2D2 (calcium channel blockers), MME (omapatrilat), ADRA2B ( $\beta$ -blockers), SLC14A2 (nifedipine), and PDE5A (sildenafil) have been identified using this approach (62). Taken together, the preceding observations are consistent with the utility of GWAS in identifying authentic druggable targets for CKDs.

Nevertheless drug discovery strategies that strictly rely on genetics may miss relevant targets. The recent SONAR trial of the endothelin receptor antagonist atrasentan in diabetic kidney disease showed a striking benefit in reducing kidney failure altogether (64). Although genetic variants at the endothelin locus associate strongly with coronary artery disease, BP, and other phenotypic traits kidney disease was not among these traits (65). This experience underscores the necessity for understanding the potential pathophysiologic relevance of each gene identified through genetic approaches, without which the utility of an implicated gene as a drug target is lacking. Conversely, lack of a genetic link should not be considered a rationale for failing to pursue a CKD target.

A major resource available to pharmaceutical companies is access to patients and samples from relatively large phase-3 kidney trials linked to hard outcomes (ESKD, death, and creatinine doubling). Although these sample sizes are insufficient for GWAS, they do allow for more limited exploration including the use of Mendelian randomization to test the causative association between biomarkers and outcomes. Focused study of genetic polymorphisms linked to drug mechanism of action has been used to identify VEGFR2 genotypes that are associated with outcome efficacy of tyrosine kinase inhibitors in renal cell cancer (87). Similar approaches might be taken in exploring efficacy of novel therapies linked to kidney outcomes in subpopulations with polymorphisms in the targeted molecule. Recent availability of resources linking genetic polymorphisms to variation in the human plasma proteins and their association with eGFR provide a tantalizing opportunity to identify novel drug targets. One can further explore causality of plasma protein level variation to kidney disease through Mendelian randomization studies (Figure 1) (88).

### Mendelian Randomization for Biomarker Validation

Genetics may also be used to test therapeutic hypotheses. The possibility that interventions to reduce uric acid levels (*e.g.*, with allopurinol) might slow diabetic nephropathy has attracted substantial attention and is under current investigation in clinical trials (66). Mendelian randomization assumes that inherited genetic variants affecting levels of a biomarker (*e.g.*, serum uric acid) can be used as variables randomized at conception that can affect an outcome (*e.g.*, CKD). Common genetic variants can therefore be used as an instrument to assess causal relationships of biomarkers while minimizing the likelihood of reverse causation (67). Recently, the role of uric acid in diabetic kidney disease progression has been explored using polymorphisms in uric acid transporters. Polymorphisms in SLC2A9 (Glut9), SLC22A11 (OAT4), SLC22A12 (URAT1 or OAT4L), and ABCG2 account for up to approximately 5% of the variability in uric acid levels (68) and as the genetic risk score increases, so does the population mean uric acid (69). These genetic studies concluded that greater uric acid levels either did not predict risk for CKD (70) or in fact may be associated with higher rather than reduced eGFR (69). The results appear to presage findings from the recently completed negative PERL study—a randomized controlled trial of allopurinol versus placebo to prevent GFR loss in patients with type 1 diabetes mellitus—which found that, despite significantly reducing uric acid, allopurinol failed to improve either GFR loss or albuminuria in type 1 diabetes mellitus (66,71).

### Apo L1 and CKD

The presence of an apo L1 (APOL1) variant in people of African descent carries one of the strongest associations with CKD for common genetic variation with a complex disease (odds ratios of 17 for FSGS and >30 for HIV-associated nephropathy) (72). APOL1 is the plasma-endogenous lytic factor for trypanosomes which induces lysis by increasing lysosomal ion leak (73). Trypanolytic APOL1 protein is primarily synthesized by the liver (74) and is constitutively secreted into the circulation as part of a minor class of HDL particles. The disease-associated polymorphisms confer activity against otherwise APOL1-resistant trypanosomal strains which predominate in western Africa.

On the surface, drug targeting of APOL1-associated kidney disease would appear highly attractive. APOL1 polymorphisms themselves are not a disease. Despite their presence from birth, emergence of kidney disease occurs only in a subset of people with APOL1 risk polymorphisms (*i.e.*, incomplete penetrance of the trait), often later in adulthood, consistent with an environmental trigger often associated with a viral illness for kidney disease to emerge (75). Furthermore, the APOL1 gene is only present in humans and a few primates but not chimpanzees or most other species including rodents. Lack of rodent or lower primate orthologs of APOL1 significantly hampers preclinical investigation of APOL1 function. Humanized mouse models have been developed but have not been fully validated with respect to accurately modeling human kidney disease pathogenesis (76–78). Finally, the cellular pathogenesis of APOL1 kidney injury remains incompletely defined with altered partitioning to cytoplasmic lipid droplets, cellular potassium ion depletion, activation of

stress-associated kinases, and impaired mitochondrial function all implicated in the cytotoxic effects of APOL1 risk variants (79–81). Which of these specific steps is optimal for therapeutic intervention remains unclear. Novel gene therapy approaches or RNA interference may provide novel and feasible approaches to mitigate disease in these patients (76).

### IgA Nephropathy

GWAS studies should also prove informative for drug development in IgA nephropathy. IgA nephropathy is the most common form of GN and a major cause of ESKD, particularly in Asia (82). In contrast to CKD and diabetic kidney disease, the diagnosis of IgA nephropathy is typically made only after kidney biopsy and it is these subjects who are included in the GWAS cohorts for IgA nephropathy. GWAS identifies several polymorphisms in the HLA locus, the complement pathway (CFHR1 and CFHR3), the B-cell trophic factor APRIL, and defensin polymorphisms, consistent with an autoimmune pathogenesis of this disease (83,84). These findings further substantiate a strategy for directing therapy at modulation of complement. Therapeutics are being developed for this indication (85).

It is notable that distinct, nonoverlapping genetic polymorphisms are associated with IgA nephropathy versus diabetic kidney disease (56,83). Although IgA nephropathy GWAS identified polymorphisms of complement factor H, the major histocompatibility locus, and defensin-A, these genes were not identified in diabetic kidney disease GWAS. Conversely, polymorphisms near UMOD and PRKAG2 emerged for kidney function in diabetic kidney disease but not for IgA nephropathy. These differences could underscore the distinct pathophysiology of the two diseases. Alternatively, these differences might be due to differences in the diagnostic criteria for inclusion in GWAS for IgA nephropathy versus diabetic kidney disease (kidney biopsy findings for IgA nephropathy versus increased serum creatinine or albuminuria for diabetic kidney disease) (13,86). Because most patients with IgA nephropathy remit and only a minority of patients with IgA nephropathy progress to ESKD, a more appropriate comparison to the diabetic kidney disease GWAS would be to limit inclusion only to the subset of patients with IgA nephropathy whose kidney function deteriorates; however, the sample size for this would likely be inadequate to power GWAS. Conversely, a GWAS on biopsy-proven diabetic kidney disease irrespective of kidney function might provide a more relevant comparison to the IgA nephropathy GWAS, but access to the necessary number of people with biopsied diabetic kidney disease seems unlikely. Nevertheless, the likelihood that distinct pathophysiology drives CKD progression in these two diseases must be considered when developing therapies.

### Reasons for Optimism: New Modalities, but New Challenges

Ascribing function to genes identified by GWAS remains a significant challenge, but tools to do so are continuing to evolve. The vast majority of disease-association signals are noncoding and likely affect gene regulation in specific disease-relevant tissues and cells; thus, understanding

cellular context (89), the epigenome, and three-dimensional chromatin architecture will be critical to advance target identification from genetics as exemplified by distant effects of noncoding polymorphisms on endothelin-1 expression or the FTO locus (65,90). The continued evolution of genomic technologies such as CRISPR gene editing (91), proteomics, single-cell and next-generation sequencing (92), induced pluripotent stem cells, and organoids (93) are continuously expanding the tools available for drug discovery. Some emerging technologies such as CRISPR and stem cell-derived cell types hold potential as therapeutic modalities in addition to their use as research tools (94). However, drug discovery and development are extremely challenging and advancing a novel modality to an approved therapy can take well beyond a decade (95) and is influenced by prevailing regulatory environment and patient circumstance, even for established modalities such as small molecules, peptides, and monoclonal antibodies. Challenges for novel modalities not previously tested in humans include off-target toxicity concerns, establishing a regulatory approval path, supply chain and manufacturing reliability, and anticipating and navigating the commercial landscape at launch and beyond. We have recently witnessed phase 3 success and regulatory approval of RNA interference (96) and *ex vivo* gene therapy (97) as well as the emergence of promising technologies in base editing, gene activation (98), and targeted degradation (99). Many currently undruggable targets in kidney disease may soon become druggable by harnessing a toolbox to replace defective genes, turn on cellular functions, or perturb systems with robust target validation from human genetics. Progress is on the horizon for several novel therapeutic modalities and, although delivery challenges are ever present, there is reason for optimism about the potential to harness recent innovation to deliver transformative medicines to patients with kidney disease.

#### Disclosures

Dr. Breyer and Dr. Reilly are full-time employees of Janssen Pharmaceutical Company.

#### References

- Herper M: The truly staggering cost of inventing new drugs. *Forbes*, 2012. Available at: <https://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/#7084d9ab4a94>. Accessed February 21, 2020
- DiMasi JA, Grabowski HG, Hansen RW: Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ* 47: 20–33, 2016
- Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, Cardon LR, Whittaker JC, Sanseau P: The support of human genetic evidence for approved drug indications. *Nat Genet* 47: 856–860, 2015
- Cohen JC, Boerwinkle E, Mosley TH Jr., Hobbs HH: Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 354: 1264–1272, 2006
- Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K; EMILIA Study Group: Trastuzumab emtansine for HER2-positive advanced breast cancer [published correction appears in *N Engl J Med* 368: 2442, 2013]. *N Engl J Med* 367: 1783–1791, 2012
- Vogelstein B, Kinzler KW: The path to cancer --three strikes and you're out. *N Engl J Med* 373: 1895–1898, 2015
- Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR: K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 359: 1757–1765, 2008
- Stein EA, Mellis S, Yancopoulos GD, Stahl N, Logan D, Smith WB, Lisbon E, Gutierrez M, Webb C, Wu R, Du Y, Kranz T, Gasparino E, Swergold GD: Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med* 366: 1108–1118, 2012
- Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, Fuster V, Boerwinkle E, Melander O, Orho-Melander M, Ridker PM, Kathiresan S: Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med* 375: 2349–2358, 2016
- Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, Hall T, Troquay RP, Turner T, Visseren FL, Wijngaard P, Wright RS, Kastelein JJ: Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med* 376: 1430–1440, 2017
- Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buyschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeier J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissono D, Siscovick D, Elousa R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S: Plasma HDL cholesterol and risk of myocardial infarction: A mendelian randomisation study. *Lancet* 380: 572–580, 2012
- Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, Voros S, Giugliano RP, Davey Smith G, Fazio S, Sabatine MS: Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med* 375: 2144–2153, 2016
- Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, Tin A, Wang L, Chu AY, Hoppmann A, Kirsten H, Giri A, Chai JF, Sveinbjornsson G, Tayo BO, Nutile T, Fuchsberger C, Marten J, Cocca M, Ghasemi S, Xu Y, Horn K, Noce D, van der Most PJ, Sedaghat S, Yu Z, Akiyama M, Afaq S, Ahluwalia TS, Almgren P, Amin N, Ärnlöv J, Bakker SJL, Bansal N, Baptista D, Bergmann S, Biggs ML, Biino G, Boehnke M, Boerwinkle E, Boissel M, Bottinger EP, Boutin TS, Brenner H, Brumat M, Burkhardt R, Butterworth AS, Campana E, Campbell A, Campbell H, Canouil M, Carroll RJ, Catamo E, Chambers JC, Chee ML, Chee ML, Chen X, Cheng CY, Cheng Y, Christensen K, Cifkova R, Ciullo M, Concas MP, Cook JP, Coresh J, Corre T, Sala CF, Cusi D, Danesh J, Daw EW, de Borst MH, De Grandi A, de Mutsert R, de Vries APJ, Degenhardt F, Delgado G, Demirkan A, Di Angelantonio E, Dittrich K, Divers J, Dorajoo R, Eckardt KU, Ehret G, Elliott P, Endlich K, Evans MK, Felix JF, Foo VH, Franco OH, Franke A, Freedman BI, Freitag-Wolf S, Friedlander Y, Froguel P, Gansevoort RT, Gao H, Gasparini P, Gaziano JM, Giedraitis V, Gieger C, Grotto G, Giulianini F, Gögele M, Gordon SD, Gudbjartsson DF, Gudnason V, Haller T, Hamet P, Harris TB, Hartman CA, Hayward C, Hellwege JN, Heng CK, Hicks AA, Hofer E, Huang W, Hutri-Kähönen N, Hwang SJ, Ikrum MA, Indridason OS, Ingelsson E, Ising M, Jaddoe VVW, Jakobsdottir J, Jonas JB, Joshi PK, Josyula NS, Jung B, Kähönen M, Kamatani Y, Kammerer CM, Kanai M, Kastarinen M, Kerr SM, Khor CC, Kiess W, Kleber ME, Koenig W, Kooner JS, Körner A, Kovacs P,

- Kraja AT, Krajcoviechova A, Kramer H, Krämer BK, Kronenberg F, Kubo M, Kühnel B, Kuokkanen M, Kuusisto J, La Bianca M, Laakso M, Lange LA, Langefeld CD, Lee JJ, Lehne B, Lehtimäki T, Lieb W, Lim SC, Lind L, Lindgren CM, Liu J, Liu J, Loeffler M, Loos RJF, Lucae S, Lukas MA, Lyytikäinen LP, Mägi R, Magnusson PKE, Mahajan A, Martin NG, Martins J, März W, Mascialzoni D, Matsuda K, Meisinger C, Meitinger T, Melander O, Metspalu A, Mikaelssdottir EK, Milaneshi Y, Miliku K, Mishra PP, Mohlke KL, Mononen N, Montgomery GW, Mook-Kanamori DO, Mychaleckyj JC, Nadkarni GN, Nalls MA, Nauck M, Nikus K, Ning B, Nolte IM, Noordam R, O'Connell J, O'Donoghue ML, Olafsson I, Oldehinkel AJ, Orho-Melander M, Ouwehand WH, Padmanabhan S, Palmer ND, Palsson R, Penninx BWJH, Perls T, Perola M, Pirastu M, Pirastu N, Pistis G, Podgornaia AI, Polasek O, Ponte B, Porteous DJ, Poulain T, Pramstaller PP, Preuss MH, Prins BP, Province MA, Rabelink TJ, Raffield LM, Raitakari OT, Reilly DF, Rettig R, Rheinberger M, Rice KM, Ridker PM, Rivadeneira F, Rizzi F, Roberts DJ, Robino A, Rossing P, Rudan I, Rueedi R, Ruggiero D, Ryan KA, Saba Y, Sabanayagam C, Salomaa V, Salvi E, Saum KU, Schmidt H, Schmidt R, Schöttker B, Schulz CA, Schupf N, Shaffer CM, Shi Y, Smith AV, Smith BH, Soranzo N, Spracklen CN, Strauch K, Stringham HM, Stumvoll M, Svensson PO, Szymczak S, Tai ES, Tajuddin SM, Tan NYQ, Taylor KD, Teren A, Tham YJ, Thiery J, Thio CHL, Thomsen H, Thorleifsson G, Toniolo D, Tönjes A, Tremblay J, Tzoulaki I, Uitterlinden AG, Vaccargiu S, van Dam RM, van der Harst P, van Duijn CM, Velez Edward DR, Verweij N, Vogelesang S, Völker U, Vollenweider P, Waeber G, Waldenberger M, Wallentin L, Wang YX, Wang C, Waterworth DM, Bin Wei W, White H, Whitfield JB, Wild SH, Wilson JF, Wojczynski MK, Wong C, Wong TY, Xu L, Yang Q, Yasuda M, Yerges-Armstrong LM, Zhang W, Zonderman AB, Rotter JJ, Bochud M, Psaty BM, Vitart V, Wilson JG, Dehghan A, Parsa A, Chasman DI, Ho K, Morris AP, Devuyst O, Akilesh S, Pendergrass SA, Sim X, Böger CA, Okada Y, Edwards TL, Snieder H, Stefansson K, Hung AM, Heid IM, Scholz M, Teumer A, Köttgen A, Pattaro C; Lifelines Cohort Study; V. A. Million Veteran Program: A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet* 51: 957–972, 2019
14. Corneec-Le Gall E, Alam A, Perrone RD: Autosomal dominant polycystic kidney disease. *Lancet* 393: 919–935, 2019
  15. Sadowski CE, Lovric S, Ashraf S, Pabst WL, Gee HY, Kohl S, Engelmann S, Vega-Warner V, Fang H, Halbritter J, Somers MJ, Tan W, Shril S, Fessi I, Lifton RP, Bockenhauer D, El-Desoky S, Kari JA, Zenker M, Kemper MJ, Mueller D, Fathy HM, Soliman NA, Hildebrandt F; SRNS Study Group: A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. *J Am Soc Nephrol* 26: 1279–1289, 2015
  16. Warejko JK, Tan W, Daga A, Schapiro D, Lawson JA, Shril S, Lovric S, Ashraf S, Rao J, Hermle T, Jobst-Schwan T, Widmeier E, Majmundar AJ, Schneider R, Gee HY, Schmidt JM, Vivante A, van der Ven AT, Ityel H, Chen J, Sadowski CE, Kohl S, Pabst WL, Nakayama M, Somers MJG, Rodig NM, Daouk G, Baum M, Stein DR, Ferguson MA, Traum AZ, Soliman NA, Kari JA, El Desoky S, Fathy H, Zenker M, Bakkaloglu SA, Müller D, Noyan A, Ozaltin F, Cadnapaphornchai MA, Hashmi S, Hopcian J, Kopp JB, Benador N, Bockenhauer D, Bogdanovic R, Stajic N, Chernin G, Ettenger R, Fehrenbach H, Kemper M, Munarriz RL, Podracka L, Büscher R, Serdaroglu E, Tasic V, Mane S, Lifton RP, Braun DA, Hildebrandt F: Whole exome sequencing of patients with steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol* 13: 53–62, 2018
  17. Funk SD, Lin MH, Miner JH: Alport syndrome and Pierson syndrome: Diseases of the glomerular basement membrane. *Matrix Biol* 71-72: 250–261, 2018
  18. Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, Li Y, Zhang J, Nestor J, Krithivasan P, Lam WY, Mitroiti A, Piva S, Kil BH, Chatterjee D, Reingold R, Bradbury D, DiVecchia M, Snyder H, Mu X, Mehl K, Balderes O, Fasel DA, Weng C, Radhakrishnan J, Canetta P, Appel GB, Bombach AS, Ahn W, Uy NS, Alam S, Cohen DJ, Crew RJ, Dube GK, Rao MK, Kamalakaran S, Copeland B, Ren Z, Bridgers J, Malone CD, Mebane CM, Dagaonkar N, Fellström BC, Haefliger C, Mohan S, Sanna-Cherchi S, Kiryluk K, Fleckner J, March R, Platt A, Goldstein DB, Gharavi AG: Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med* 380: 142–151, 2019
  19. Welsh MJ, Liedtke CM: Chloride and potassium channels in cystic fibrosis airway epithelia. *Nature* 322: 467–470, 1986
  20. Quinton PM: Chloride impermeability in cystic fibrosis. *Nature* 301: 421–422, 1983
  21. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsky N, Chou JL, Drumm ML, Lannuzzi MC, Collins FS, Tsui LC: Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA [published correction appears in *Science* 245: 1437, 1989]. *Science* 245: 1066–1073, 1989
  22. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, Wang LT, Ingenito EP, McKee C, Lu Y, Lekstrom-Himes J, Elborn JS: Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *N Engl J Med* 377: 2013–2023, 2017
  23. Winn MP, Conlon PJ, Lynn KL, Farrington MK, Creazzo T, Hawkins AF, Daskalakis N, Kwan SY, Ebersviller S, Burchette JL, Pericak-Vance MA, Howell DN, Vance JM, Rosenberg PB: A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. *Science* 308: 1801–1804, 2005
  24. Reiser J, Polu KR, Möller CC, Kenlan P, Altintas MM, Wei C, Faul C, Herbert S, Villegas I, Avila-Casado C, McGee M, Sugimoto H, Brown D, Kalluri R, Mundel P, Smith PL, Clapham DE, Pollak MR: TRPC6 is a glomerular slit diaphragm-associated channel required for normal renal function. *Nat Genet* 37: 739–744, 2005
  25. Eckel J, Lavin PJ, Finch EA, Mukerji N, Burch J, Gbadegesin R, Wu G, Bowling B, Byrd A, Hall G, Sparks M, Zhang ZS, Homstad A, Barisoni L, Birbaumer L, Rosenberg P, Winn MP: TRPC6 enhances angiotensin II-induced albuminuria. *J Am Soc Nephrol* 22: 526–535, 2011
  26. Kim JH, Xie J, Hwang KH, Wu YL, Oliver N, Eom M, Park KS, Barrezaeta N, Kong ID, Fracasso RP, Huang CL, Cha SK: Klotho may ameliorate proteinuria by targeting TRPC6 channels in podocytes. *J Am Soc Nephrol* 28: 140–151, 2017
  27. Zhou Y, Castonguay P, Sidhom EH, Clark AR, Dvela-Levitt M, Kim S, Sieber J, Wieder N, Jung JY, Andreeva S, Reichardt J, Dubois F, Hoffmann SC, Basgen JM, Montesinos MS, Weins A, Johnson AC, Lander ES, Garrett MR, Hopkins CR, Greka A: A small-molecule inhibitor of TRPC5 ion channels suppresses progressive kidney disease in animal models. *Science* 358: 1332–1336, 2017
  28. Beitelshoes AL, Leslie BR, Taylor SI: Sodium-glucose cotransporter 2 inhibitors: A case study in translational research. *Diabetes* 68: 1109–1120, 2019
  29. Marble A: The diagnosis of the less common meliturias; including pentosuria and fructosuria. *Med Clin North Am* 31: 313–325, 1947
  30. Elsas LJ, Rosenberg LE: Familial renal glycosuria: A genetic reappraisal of hexose transport by kidney and intestine. *J Clin Invest* 48: 1845–1854, 1969
  31. Oemar BS, Byrd DJ, Brodehl J: Complete absence of tubular glucose reabsorption: A new type of renal glucosuria (type 0). *Clin Nephrol* 27: 156–160, 1987
  32. Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M, Brodehl J, Daschner M, Ehrich JH, Kemper M, Li Volti S, Neuhaus T, Skovby F, Swift PG, Schaub J, Klaerke D: Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* 14: 2873–2882, 2003
  33. Calado J, Sznajder Y, Metzger D, Rita A, Hogan MC, Kattamis A, Scharf M, Tasic V, Greil J, Brinkert F, Kemper MJ, Santer R: Twenty-one additional cases of familial renal glucosuria: Absence of genetic heterogeneity, high prevalence of private mutations and further evidence of volume depletion. *Nephrol Dial Transplant* 23: 3874–3879, 2008
  34. Scholl-Bürgi S, Santer R, Ehrich JH: Long-term outcome of renal glucosuria type 0: The original patient and his natural history. *Nephrol Dial Transplant* 19: 2394–2396, 2004
  35. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CRENDENCE Trial Investigators: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 380: 2295–2306, 2019
  36. Ehrenkranz JR, Lewis NG, Kahn CR, Roth J: Phlorizin: A review. *Diabetes Metab Res Rev* 21: 31–38, 2005

37. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Matthews M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators: Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 375: 323–334, 2016
38. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group: Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 377: 644–657, 2017
39. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE-TIMI 58 Investigators: Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 380: 347–357, 2019
40. O'Donnell CJ, Nabel EG: Cardiovascular genomics, personalized medicine, and the National Heart, Lung, and Blood Institute: Part I: The beginning of an era. *Circ Cardiovasc Genet* 1: 51–57, 2008
41. Altshuler D, Daly MJ, Lander ES: Genetic mapping in human disease. *Science* 322: 881–888, 2008
42. van Zuydam NR, Ahlqvist E, Sandholm N, Deshmukh H, Rayner NW, Abdalla M, Ladenvall C, Ziemek D, Fauman E, Robertson NR, McKeigue PM, Valo E, Forsblom C, Harjutsalo V, Perna A, Rurali E, Marcovecchio ML, Igo RP Jr., Salem RM, Perico N, Lajer M, Käräjämäki A, Imamura M, Kubo M, Takahashi A, Sim X, Liu J, van Dam RM, Jiang G, Tam CHT, Luk AOY, Lee HM, Lim CKP, Szeto CC, So WY, Chan JCN, Ang SF, Dorajoo R, Wang L, Clara TSH, McKnight AJ, Duffy S, Pezzolesi MG, Marre M, Gyorgy B, Hadjadj S, Hiraki LT, Ahluwalia TS, Almgren P, Schulz CA, Orho-Melander M, Linneberg A, Christensen C, Witte DR, Grarup N, Brandslund I, Melander O, Paterson AD, Tregouet D, Maxwell AP, Lim SC, Ma RCW, Tai ES, Maeda S, Lyssenko V, Tuomi T, Krolewski AS, Rich SS, Hirschhorn JN, Florez JC, Dunger D, Pedersen O, Hansen T, Rossing P, Remuzzi G, Brosnan MJ, Palmer CNA, Groop PH, Colhoun HM, Groop LC, McCarthy MI; Finnish Diabetic Nephropathy Study (FinnDiane); Hong Kong Diabetes Registry Theme-based Research Scheme Project Group; Warren 3 and Genetics of Kidneys in Diabetes (GoKinD) Study Group; GENIE (Genetics of Nephropathy an International Effort) Consortium; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group; SURrogate markers for Micro- and Macrovascular hard endpoints for Innovative diabetes Tools (SUMMIT) Consortium: A genome-wide association study of diabetic kidney disease in subjects with type 2 diabetes. *Diabetes* 67: 1414–1427, 2018
43. Köttgen A, Glazer NL, Dehghan A, Hwang SJ, Katz R, Li M, Yang Q, Gudnason V, Launer LJ, Harris TB, Smith AV, Arking DE, Astor BC, Boerwinkle E, Ehret GB, Ruczinski I, Scharpf RB, Chen YD, de Boer IH, Haritunians T, Lumley T, Sarnak M, Siscovick D, Benjamin EJ, Levy D, Upadhyay A, Aulchenko YS, Hofman A, Rivadeneira F, Uitterlinden AG, van Duijn CM, Chasman DI, Paré G, Ridker PM, Kao WH, Witteman JC, Coresh J, Shlipak MG, Fox CS: Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* 41: 712–717, 2009
44. Tamm I, Horsfall FL Jr.: A mucoprotein derived from human urine which reacts with influenza, mumps, and Newcastle disease viruses. *J Exp Med* 95: 71–97, 1952
45. Rindler MJ, Naik SS, Li N, Hoops TC, Peraldi MN: Uromodulin (Tamm-Horsfall glycoprotein/uromucoid) is a phosphatidylinositol-linked membrane protein. *J Biol Chem* 265: 20784–20789, 1990
46. Köttgen A, Hwang SJ, Larson MG, Van Eyk JE, Fu Q, Benjamin EJ, Dehghan A, Glazer NL, Kao WH, Harris TB, Gudnason V, Shlipak MG, Yang Q, Coresh J, Levy D, Fox CS: Uromodulin levels associate with a common UMOD variant and risk for incident CKD. *J Am Soc Nephrol* 21: 337–344, 2010
47. Olden M, Corre T, Hayward C, Toniolo D, Ulivi S, Gasparini P, Pistis G, Hwang SJ, Bergmann S, Campbell H, Cocca M, Gandin I, Grotto G, Glaudemans B, Hastie ND, Loffing J, Polasek O, Rampoldi L, Rudan I, Sala C, Traglia M, Vollenweider P, Vuckovic D, Youhanna S, Weber J, Wright AF, Kutalik Z, Bochud M, Fox CS, Devuyst O: Common variants in UMOD associate with urinary uromodulin levels: A meta-analysis. *J Am Soc Nephrol* 25: 1869–1882, 2014
48. Hession C, Decker J, Sherblom A, Kumar S, Yue C, Mattaliano R, Tizard R, Kawashima E, Schmeissner U, Heletky S, Chow EP, Burne CA, Shaw A, Muchmore AV: Uromodulin (Tamm-Horsfall glycoprotein): a renal ligand for lymphokines. *Science* 237: 1479–1484, 1987
49. Trudu M, Janas S, Lanzani C, Debaix H, Schaeffer C, Ikehata M, Citterio L, Demaretz S, Trevisani F, Ristagno G, Glaudemans B, Laghmani K, Dell'Antonio G, Loffing J, Rastaldi MP, Manunta P, Devuyst O, Rampoldi L; SKIPOGH team: Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med* 19: 1655–1660, 2013
50. Edwards N, Olinger E, Adam J, Kelly M, Schiano G, Ramsbottom SA, Sandford R, Devuyst O, Sayer JA: A novel homozygous UMOD mutation reveals gene dosage effects on uromodulin processing and urinary excretion. *Nephrol Dial Transplant* 32: 1994–1999, 2017
51. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D; Diabetes Prevention Program Research Group: TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. *N Engl J Med* 355: 241–250, 2006
52. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadóttir A, Styrkarsdóttir U, Magnusson KP, Walters GB, Palsdóttir E, Jonsdóttir T, Gudmundsdóttir T, Gylfason A, Saemundsdóttir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdóttir U, Gulcher JR, Kong A, Stefansson K: Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 38: 320–323, 2006
53. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261: 921–923, 1993
54. Salem RM, Todd JN, Sandholm N, Cole JB, Chen W-M, Andrews D, Pezzolesi MG, McKeigue PM, Hiraki LT, Qiu C, Nair V, Di Liao C, Jing Cao J, Valo E, Onengut-Gumuscu S, Smiles AM, McGurnaghan SJ, Haukka JK, Harjutsalo V, Brennan EP, van Zuydam N, Ahlqvist E, Doyle R, Ahluwalia TS, Lajer M, Hughes MF, Park J, Skupien J, Spiliopoulou A, Liu A, Menon R, Boustany-Kari CM, Kang HM, Nelson RG, Klein R, Klein BE, Lee KE, Gao X, Mauer M, Maeaestroni S, Luiza Caramori M, de Boer IH, Miller RG, Guo J, Borigt AP, Tregouet D, Gyorgy B, Snell-Bergeon JK, Maahs DM, Bull SB, Canty AJ, Palmer CNA, Stechemesser L, Paulweber B, Weitgasser R, Sokolovska J, Rovite V, Pīrāgs V, Prakiene E, Radzeviciene L, Verkauskiene R, Mircea Panduru N, Groop LC, McCarthy MI, Gu HF, Möllsten A, Falhammar H, Brismar K, Martin F, Rossing P, Costacou T, Zerbini G, Marre M, Hadjadj S, McKnight AJ, Forsblom C, McKay G, Godson C, Maxwell AP, Kretzler M, Susztak K, Colhoun HM, Krolewski A, Paterson AD, Groop P-H, Rich SS, Hirschhorn JN, Florez JC; GENIE Consortium, DCCT/EDIC Research Group, SUMMIT Consortium: Genome-wide association study of diabetic kidney disease highlights biology involved in renal basement membrane collagen. *J Am Soc Nephrol* 30: 2000–2016, 2019
55. Anders HJ, Huber TB, Isermann B, Schiffer M: CKD in diabetes: Diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol* 14: 361–377, 2018
56. Pattaro C, Teumer A, Gorski M, Chu AY, Li M, Mijatovic V, Garnaas M, Tin A, Sorice R, Li Y, Taliun D, Olden M, Foster M, Yang Q, Chen MH, Pers TH, Johnson AD, Ko YA, Fuchsberger C, Tayo B, Nalls M, Feitosa MF, Isaacs A, Dehghan A, d'Adamo P, Adeyemo A, Dieffenbach AK, Zonderman AB, Nolte IM, van der Most PJ, Wright AF, Shuldiner AR, Morrison AC, Hofman A, Smith AV, Dreisbach AW, Franke A, Uitterlinden AG, Metspalu A, Tonjes A, Lupo A, Robino A, Johansson A, Demirkan K, Kollerits B, Freedman BI, Ponte B, Oostra BA, Paulweber B, Krämer BK, Mitchell BD, Buckley BM, Peralta CA, Hayward C, Helmer C, Rotimi CN, Shaffer CM, Müller C, Sala C, van Duijn CM, Saint-Pierre A, Ackermann D, Shriver D, Ruggiero D, Toniolo D, Lu Y, Cusi D, Czamara D, Ellinghaus D, Siscovick DS, Ruderfer D, Gieger C, Grallert H, Rohtchina E, Atkinson EJ, Holliday EG, Boerwinkle E, Salvi E, Bottinger EP, Murgia F, Rivadeneira F, Ernst F, Kronenberg F, Hu FB, Navis GJ, Curhan GC, Ehret GB, Homuth G, Coassin S, Thun GA, Pistis G, Gambaro G, Malerba G,



- Montgomery GW, Eiriksdottir G, Jacobs G, Li G, Wichmann HE, Campbell H, Schmidt H, Wallaschofski H, Völzke H, Brenner H, Kroemer HK, Kramer H, Lin H, Leach IM, Ford I, Guessous I, Rudan I, Prokopenko I, Borecki I, Heid IM, Kolcic I, Persico I, Jukema JW, Wilson JF, Felix JF, Divers J, Lambert JC, Stafford JM, Gaspoz JM, Smith JA, Faul JD, Wang JJ, Ding J, Hirschhorn JN, Attia J, Whitfield JB, Chalmers J, Viikari J, Coresh J, Denny JC, Karjalainen J, Fernandes JK, Endlich K, Butterbach K, Keene KL, Lohman K, Portas L, Launer LJ, Lyytikäinen LP, Yengo L, Franke L, Ferrucci L, Rose LM, Kedenko L, Rao M, Struchalin M, Kleber ME, Cavalieri M, Haun M, Cornelis MC, Ciullo M, Pirastu M, de Andrade M, McEvoy MA, Woodward M, Adam M, Cocca M, Nauck M, Imboden M, Waldenberger M, Pruijm M, Metzger M, Stumvoll M, Evans MK, Sale MM, Kähönen M, Boban M, Bochud M, Rheinberger M, Verweij N, Bouatia-Naji N, Martin NG, Hastie N, Probst-Hensch N, Soranzo N, Devuyst O, Raitakari O, Gottesman O, Franco OH, Polasek O, Gasparini P, Munroe PB, Ridker PM, Mitchell P, Muntner P, Meisinger C, Smit JH, Kovacs P, Wild PS, Froguel P, Rettig R, Mägi R, Biffar R, Schmidt R, Middelberg RP, Carroll RJ, Penninx BW, Scott RJ, Katz R, Sedaghat S, Wild SH, Kardina SL, Ulivi S, Hwang SJ, Enroth S, Kloiber S, Trompet S, Stengel B, Hancock SJ, Turner ST, Rosas SE, Stracke S, Harris TB, Zeller T, Zemunik T, Lehtimäki T, Illig T, Aspelund T, Nikopoulou T, Esko T, Tanaka T, Gyllenstein U, Völker U, Emilsson V, Vitart V, Aalto V, Gudnason V, Chouraki V, Chen WM, Igl W, März W, Koenig W, Lieb W, Loos RJ, Liu Y, Snieder H, Pramstaller PP, Parsa A, O'Connell JR, Suszkat K, Hamet P, Tremblay J, de Boer IH, Böger CA, Goessling W, Chasman DI, Köttgen A, Kao WH, Fox CS; ICBP Consortium; AGEN Consortium; CARDIOGRAM; CHARGE-Heart Failure Group; ECHOGEN Consortium: Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. *Nat Commun* 7: 10023, 2016
57. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDESCENCE Trial Investigators: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 380: 2295–2306, 2019
58. César-Razquin A, Snijder B, Frappier-Brinton T, Isserlin R, Gyimesi G, Bai X, Reithmeier RA, Hepworth D, Hediger MA, Edwards AM, Superti-Furga G: A call for systematic research on solute carriers. *Cell* 162: 484–487, 2015
59. Fagerberg L, Hallström BM, Oksvold P, Kamp C, Djureinovic D, Odeberg J, Habuka M, Tahmasebpoor S, Danielsson A, Edlund K, Asplund A, Sjöstedt E, Lundberg E, Szilagyi CA, Skogs M, Takanan JO, Berling H, Tegel H, Mulder J, Nilsson P, Schwenk JM, Lindskog C, Danielsson F, Mardinoglu A, Sivertsson A, von Feilitzen K, Forsberg M, Zvalnen M, Olsson I, Navani S, Huss M, Nielsen J, Ponten F, Uhlén M: Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol Cell Proteomics* 13: 397–406, 2014
60. Sayed-Tabatabaei FA, Oostra BA, Isaacs A, van Duijn CM, Witteman JC: ACE polymorphisms. *Circ Res* 98: 1123–1133, 2006
61. Boright AP, Paterson AD, Mirea L, Bull SB, Mowjoodi A, Scherer SW, Zinman B; DCCT/EDIC Research Group: Genetic variation at the ACE gene is associated with persistent microalbuminuria and severe nephropathy in type 1 diabetes: The DCCT/EDIC genetics study. *Diabetes* 54: 1238–1244, 2005
62. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, Ntalla I, Surendran P, Liu C, Cook JP, Kraja AT, Drenos F, Loh M, Verweij N, Marten J, Karaman I, Lepe MP, O'Reilly PF, Knight J, Snieder H, Kato N, He J, Tai ES, Said MA, Porteous D, Alver M, Poulter N, Farrall M, Gansevoort RT, Padmanabhan S, Mägi R, Stanton A, Connell J, Bakker SJ, Metspalu A, Shields DC, Thom S, Brown M, Sever P, Esko T, Hayward C, van der Harst P, Saleheen D, Chowdhury R, Chambers JC, Chasman DI, Chakravarti A, Newton-Cheh C, Lindgren CM, Levy D, Koonen JS, Keavney B, Tomaszewski M, Samani NJ, Howson JM, Tobin MD, Munroe PB, Ehret GB, Wain LV; International Consortium of Blood Pressure (ICBP) 1000G Analyses; BIOS Consortium; Lifelines Cohort Study; Understanding Society Scientific group; CHD Exome+ Consortium; ExomeBP Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; Cohorts for Heart and Ageing Research in Genome Epidemiology (CHARGE) BP Exome Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; UK Biobank CardioMetabolic Consortium BP working group: Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet* 49: 403–415, 2017
63. Chung CM, Wang RY, Chen JW, Fann CS, Leu HB, Ho HY, Ting CT, Lin TH, Sheu SH, Tsai WC, Chen JH, Jong YS, Lin SJ, Chen YT, Pan WH: A genome-wide association study identifies new loci for ACE activity: Potential implications for response to ACE inhibitor. *Pharmacogenomics J* 10: 537–544, 2010
64. Heerspink HJL, Parving HH, Andress DL, Bakris G, Correa-Rotter R, Hou FF, Kitzman DW, Kohan D, Makino H, McMurray JJV, Melnick JZ, Miller MG, Pergola PE, Perkovic V, Tobe S, Yi T, Wiggins M, de Zeeuw D; SONAR Committees and Investigators: Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): A double-blind, randomised, placebo-controlled trial [published correction appears in *Lancet* 393: 1936, 2019]. *Lancet* 393: 1937–1947, 2019
65. Gupta RM, Hadaya J, Trehan A, Zekavat SM, Roselli C, Klarin D, Emdin CA, Hilvering CRE, Bianchi V, Mueller C, Khera AV, Ryan RJH, Engreitz JM, Issner R, Shores N, Epstein CB, de Laat W, Brown JD, Schnabel RB, Bernstein BE, Kathiresan S: A genetic variant associated with five vascular diseases is a distal regulator of endothelin-1 gene expression. *Cell* 170: 522–533.e15, 2017
66. Maahs DM, Caramori L, Cherney DZ, Galecki AT, Gao C, Jalal D, Perkins BA, Pop-Busui R, Rossing P, Mauer M, Doria A; PERL Consortium: Uric acid lowering to prevent kidney function loss in diabetes: The preventing early renal function loss (PERL) allopurinol study. *Curr Diab Rep* 13: 550–559, 2013
67. Sekula P, Del Greco M F, Pattaro C, Köttgen A: Mendelian randomization as an approach to assess causality using observational data. *J Am Soc Nephrol* 27: 3253–3265, 2016
68. Yang Q, Köttgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, Chasman DI, Aspelund T, Eiriksdottir G, Harris TB, Launer L, Nalls M, Hernandez D, Arking DE, Boerwinkle E, Grove ML, Li M, Linda Kao WH, Chonchol M, Haritunians T, Li G, Lumley T, Psaty BM, Shlipak M, Hwang SJ, Larson MG, O'Donnell CJ, Upadhyay A, van Duijn CM, Hofman A, Rivadeneira F, Stricker B, Uitterlinden AG, Paré G, Parker AN, Ridker PM, Siscovick DS, Gudnason V, Witteman JC, Fox CS, Coresh J: Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet* 3: 523–530, 2010
69. Hughes K, Flynn T, de Zoysa J, Dalbeth N, Merriman TR: Mendelian randomization analysis associates increased serum urate, due to genetic variation in uric acid transporters, with improved renal function. *Kidney Int* 85: 344–351, 2014
70. Jordan DM, Choi HK, Verbanck M, Topless R, Won HH, Nadkarni G, Merriman TR, Do R: No causal effects of serum urate levels on the risk of chronic kidney disease: A mendelian randomization study. *PLoS Med* 16: e1002725, 2019
71. Doria A, Andrzej G, Cathie S, Michael M: Preventing early renal loss in diabetes (PERL) study: Outcome of a 3-year trial of serum uric acid reduction with allopurinol. Presented at the 2019 American Society of Nephrology Kidney Week, November 7–10, 2019
72. Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, Friedman D, Briggs W, Dart R, Korbet S, Mokrzycki MH, Kimmel PL, Limou S, Ahuja TS, Berns JS, Fryc J, Simon EE, Smith MC, Trachtman H, Michel DM, Schelling JR, Vlahov D, Pollak M, Winkler CA: APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 22: 2129–2137, 2011
73. Vanhamme L, Paturiaux-Hanocq F, Poelvoorde P, Nolan DP, Lins L, Van Den Abbeele J, Pays A, Tebabi P, Van Xong H, Jacquet A, Moguilevsky N, Dieu M, Kane JP, De Baetselier P, Brasseur R, Pays E: Apolipoprotein L-I is the trypanosome lytic factor of human serum. *Nature* 422: 83–87, 2003
74. Shukha K, Mueller JL, Chung RT, Curry MP, Friedman DJ, Pollak MR, Berg AH: Most ApoL1 is secreted by the liver. *J Am Soc Nephrol* 28: 1079–1083, 2017

75. Husain SA, Chang JH: Searching for second hits for the development of *APOL1*-associated kidney disease. *Kidney Int Rep* 4: 911–913, 2019
76. Aghajani M, Booten SL, Althage M, Hart CE, Ericsson A, Maxvill I, Ochaba J, Menschik-Lundin A, Hartleib J, Kuntz S, Gattis D, Ahlström C, Watt AT, Engelhardt JA, Monia BP, Magnone MC, Guo S: Antisense oligonucleotide treatment ameliorates IFN- $\gamma$ -induced proteinuria in *APOL1*-transgenic mice. *JCI Insight* 4: 126124, 2019
77. Bruggeman LA, O'Toole JF, Sedor JR: *APOL1* polymorphisms and kidney disease: Loss-of-function or gain-of-function? *Am J Physiol Renal Physiol* 316: F1–F8, 2019
78. Beckerman P, Bi-Karchin J, Park AS, Qiu C, Dummer PD, Soomro I, Boustany-Kari CM, Pullen SS, Miner JH, Hu CA, Rohacs T, Inoue K, Ishibe S, Saleem MA, Palmer MB, Cuervo AM, Kopp JB, Susztak K: Transgenic expression of human *APOL1* risk variants in podocytes induces kidney disease in mice. *Nat Med* 23: 429–438, 2017
79. Chun J, Zhang JY, Wilkins MS, Subramanian B, Riella C, Magraner JM, Alper SL, Friedman DJ, Pollak MR: Recruitment of *APOL1* kidney disease risk variants to lipid droplets attenuates cell toxicity. *Proc Natl Acad Sci U S A* 116: 3712–3721, 2019
80. Olabisi OA, Zhang JY, VerPlank L, Zahler N, DiBartolo S 3rd, Heneghan JF, Schlöndorff JS, Suh JH, Yan P, Alper SL, Friedman DJ, Pollak MR: *APOL1* kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. *Proc Natl Acad Sci U S A* 113: 830–837, 2016
81. Shah SS, Lannon H, Dias L, Zhang JY, Alper SL, Pollak MR, Friedman DJ: *APOL1* kidney risk variants induce cell death via mitochondrial translocation and opening of the mitochondrial permeability transition pore. *J Am Soc Nephrol* 30: 2355–2368, 2019
82. Rodrigues JC, Haas M, Reich HN: IgA nephropathy. *Clin J Am Soc Nephrol* 12: 677–686, 2017
83. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, Sanna-Cherchi S, Men CJ, Julian BA, Wyatt RJ, Novak J, He JC, Wang H, Lv J, Zhu L, Wang W, Wang Z, Yasuno K, Gunel M, Mane S, Umlauf S, Tikhonova I, Beerman I, Savoldi S, Magistroni R, Ghiggeri GM, Bodria M, Lugani F, Ravani P, Ponticelli C, Allegri L, Boscutti G, Frasca G, Amore A, Peruzzi L, Coppo R, Izzi C, Viola BF, Prati E, Salvadori M, Mignani R, Gesualdo L, Bertinetto F, Mesiano P, Amoroso A, Scolari F, Chen N, Zhang H, Lifton RP: Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet* 43: 321–327, 2011
84. Yu X-Q, Li M, Zhang H, Low HQ, Wei X, Wang JQ, Sun LD, Sim KS, Li Y, Foo JN, Wang W, Li ZJ, Yin XY, Tang XQ, Fan L, Chen J, Li RS, Wan JX, Liu ZS, Lou TQ, Zhu L, Huang XJ, Zhang XJ, Liu ZH, Liu JJ: A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. *Nat Genet* 44: 178–182, 2011
85. Rizk DV, Maillard N, Julian BA, Knoppova B, Green TJ, Novak J, Wyatt RJ: The emerging role of complement proteins as a target for therapy of IgA nephropathy. *Front Immunol* 10: 504, 2019
86. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, Snyder HJ, Choi M, Hou P, Scolari F, Izzi C, Gigante M, Gesualdo L, Savoldi S, Amoroso A, Cusi D, Zamboli P, Julian BA, Novak J, Wyatt RJ, Mucha K, Perola M, Kristiansson K, Viktorin A, Magnusson PK, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Boland A, Metzger M, Thibaudin L, Wanner C, Jager KJ, Goto S, Maixnerova D, Karnib HH, Nagy J, Panzer U, Xie J, Chen N, Tesar V, Narita I, Berthoux F, Floege J, Stengel B, Zhang H, Lifton RP, Gharavi AG: Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet* 8: e1002765, 2012
87. Escudier B, Rini BI, Motzer RJ, Tarazi J, Kim S, Huang X, Rosbrook B, English PA, Loomis AK, Williams JA: Genotype correlations with blood pressure and efficacy from a randomized phase III trial of second-line axitinib versus sorafenib in metastatic renal cell carcinoma. *Clin Genitourin Cancer* 13: 328–337.e3, 2015
88. Sun BB, Maranville JC, Peters JE, Stacey D, Staley JR, Blackshaw J, Burgess S, Jiang T, Paige E, Surendran P, Oliver-Williams C, Kamat MA, Prins BP, Wilcox SK, Zimmerman ES, Chi A, Bansal N, Spain SL, Wood AM, Morrell NW, Bradley JR, Janjic N, Roberts DJ, Ouwehand WH, Todd JA, Soranzo N, Suhre K, Paul DS, Fox CS, Plenge RM, Danesh J, Runz H, Butterworth AS: Genomic atlas of the human plasma proteome. *Nature* 558: 73–79, 2018
89. Qiu C, Huang S, Park J, Park Y, Ko YA, Seasock MJ, Bryer JS, Xu XX, Song WC, Palmer M, Hill J, Guarneri P, Hawkins J, Boustany-Kari CM, Pullen SS, Brown CD, Susztak K: Renal compartment-specific genetic variation analyses identify new pathways in chronic kidney disease. *Nat Med* 24: 1721–1731, 2018
90. Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, Glunk V, Sousa IS, Beaudry JL, Puvion-Dutilleul V, Abdennur NA, Liu J, Svensson PA, Hsu YH, Drucker DJ, Mellgren G, Hui CC, Hauner H, Kellis M: FTO obesity variant circuitry and adipocyte browning in humans. *N Engl J Med* 373: 895–907, 2015
91. Cruz NM, Freedman BS: CRISPR gene editing in the kidney. *Am J Kidney Dis* 71: 874–883, 2018
92. Wilson PC, Wu H, Kirita Y, Uchimura K, Ledru N, Renke HG, Welling PA, Waikar SS, Humphreys BD: The single-cell transcriptomic landscape of early human diabetic nephropathy. *Proc Natl Acad Sci U S A* 116: 19619–19625, 2019
93. Boreström C, Jonebring A, Guo J, Palmgren H, Cederblad L, Forslöv A, Svensson A, Söderberg M, Reznichenko A, Nyström J, Patrakka J, Hicks R, Maresca M, Valastro B, Collén A: A CRISPR(e)R view on kidney organoids allows generation of an induced pluripotent stem cell-derived kidney model for drug discovery. *Kidney Int* 94: 1099–1110, 2018
94. Xu L, Wang J, Liu Y, Xie L, Su B, Mou D, Wang L, Zhang B, Zhao L, Hu L, Ning H, Zhang Y, Deng K, Liu L, Lu X, Zhang T, Xu J, Li C, Wu H, Deng H, Chen H: CRISPR-edited stem cells in a patient with HIV and acute lymphocytic leukemia. *N Engl J Med*, 381: 1240–1247, 2019
95. Setten RL, Rossi JJ, Han SP: The current state and future directions of RNAi-based therapeutics. *Nat Rev Drug Discov* 18: 421–446, 2019
96. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Planté-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH 3rd, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnav AK, Gollub JA, Suhr OB: Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 379: 11–21, 2018
97. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, Brogdon JL, Pruteanu-Malinici I, Bhoj V, Landsburg D, Wasik M, Levine BL, Lacey SF, Melenhorst JJ, Porter DL, June CH: Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med* 377: 2545–2554, 2017
98. Dominguez AA, Lim WA, Qi LS: Beyond editing: Repurposing CRISPR-cas9 for precision genome regulation and interrogation. *Nat Rev Mol Cell Biol* 17: 5–15, 2016
99. Fisher SL, Phillips AJ: Targeted protein degradation and the enzymology of degraders. *Curr Opin Chem Biol* 44: 47–55, 2018