CKJ REVIEW

Precision medicine for the treatment of glomerulonephritis: a bold goal but not yet a transformative achievement

Richard J. Glassock

Emeritus Professor, Department of Medicine, Geffen School of Medicine, Los Angeles, CA, USA

Correspondence to: Richard J. Glassock; E-mail: rjglassock@gmail.com

ABSTRACT

The revolution in our ability to recognize the alterations in fundamental biology brought about by disease has fostered a renewed interest in precision or personalized medicine ('the right treatment, or diagnostic test, for the right patient at the right time'). This nascent field has been led by oncology, immunohematology and infectious disease, but nephrology is catching up and quickly. Specific forms of glomerulonephritis (GN) thought to represent specific 'diseases' have been 'downgraded' to 'patterns of injury'. New entities have emerged through the application of sophisticated molecular technologies, often embraced by the term 'multi-omics'. Kidney biopsies are now interpreted by next-generation imaging and machine learning. Many opportunities are manifest that will translate these remarkable developments into novel safe and effective treatment regimens for specific pathogenic pathways evoking GN and its progression to kidney failure. A few successes embolden a positive look to the future. A sustained and highly collaborative engagement with this new paradigm will be required for this field, full of hope and high expectations, to realize its goal of transforming glomerular therapeutics from one size fits all (or many) to a true individualized management principle.

Keywords: genomics, glomerulonephritis, machine learning, multi-omics, precision medicine

INTRODUCTION

Precision or personalized medicine is designed to ensure that the best treatment (or diagnostic test) is applied to the right patient at the right time [1]. In a certain way, precision medicine is the antithesis of clinical practice guidelines (CPGs). The latter approaches deal largely with the average patient rather than with the individual patient. The application of many current CPGs to individual patients can be challenging due to the phenotypic and biological variability among specific diseases, including glomerulonephritis (GN). However, elements of a precision medicine approach are slowly being incorporated into CPGs for GN. In addition, we have learned that some diseases are in reality 'patterns of injury' with a great deal of hidden heterogeneity of underlying pathogenesis [2] only uncovered when sophisticated methods of analysis are applied to dissect this cloaked diversity. It is presumed that a treatment directed to a specific target known to be involved in the pathogenesis of a specific disease entity will have an intrinsic advantage for altering the natural history of disease, perhaps in a safer manner, than empiric therapy.

Thus the rationale underlying precision or personalized medicine and its opportunities and potential benefits are well understood. The nascent field of precision medicine received a considerable boost when then-President Barack Obama included it as one of his forward-looking initiatives in his State of the Union address to the US Congress on 20 January 2015 [3]. Of course, precision medicine is not new, having been practiced

since the early 20th century in the form of erythrocyte typing for blood transfusion [4], treating breast cancer on the basis of receptors found in excised tissue and managing infections based on *in vitro* testing of sensitivity to antimicrobial agents. Indeed, medical oncology, immunohematology and infectious disease specialists were early adopters of a precision-based approach to medical care, and the results, in terms of outcomes, have been phenomenal, especially concerning the application of advances in molecular genetics to specific disease states.

To facilitate and broaden the reach of a national goal of precision medicine, the All of Us research project was created by the National Institutes of Health (NIH) to enroll ≥1 million subjects in order to create a database for the enhancement of precision medicine projects [5]. While the initial focus of this initiative was on cancer, it has spread to include kidney disease in very important ways and spawned many novel approaches to the application of precision medicine in, in particular, glomerular disease. The 100 000 Genomes Project of the UK National Health Service is another example of how precision medicine based on genomic analysis can help augment the correct diagnosis of rare diseases, including those involving the kidney [6], thus providing new approaches to precision testing, and hopefully personalized therapy. The overarching purpose of this brief review is to examine the current status of precision medicine in the management of several forms of GN, to consider the problems and obstacles challenging success in this new field and to lay out a possible road map for the future.

## CURRENT INITIATIVES OF KIDNEY-SPECIFIC PRECISION MEDICINE

While one might regard many avenues of research as directly impinging on the practice of precision medicine in kidney disease, such as 'deep phenotyping', unbiased hierarchical cluster analysis and genome-based diagnosis [7], only a few will be discussed here. The Kidney Precision Medicine Project (KPMP), sponsored by the NIH and inaugurated in 2017 after a landmark workshop held in 2016, recommended that a new initiative be launched [8]. The KPMP seeks to 'redefine chronic kidney disease (CKD) and acute kidney injury (AKI) by "integrating deep molecular phenotyping," employing clinical characterization, digital pathology of kidney biopsies and clinical outcomes analysis' [8]. The unique aspect of this project is that the acquisition of the molecular pathologic profile of CKD and AKI developed from research protocol kidney biopsies will be linked to specific outcomes to identify critical pathways and targets for novel therapies. Novel methods of molecular analysis (multi-omics), digital pathology, imaging technology and bioinformatics will be employed. Integration of patient priorities and community engagement has been a highlight of this project since its beginning [9, 10]. While it is anticipated that GN will be among the diseases studied, the initial focus will be on diabetic nephropathy and AKI. The project has been thoroughly and exhaustively designed, with due respect for safety, ethical issues, feasibility and acceptance by willing participants [11]. A pilot trial anticipating the enrollment of ∽200 participants has commenced. Preliminary results are beginning to appear in the published literature [11, 12]. The role of artificial intelligence (AI) and machine learning (ML) analysis of the 'big data' generated from this and other similar studies will be crucial for the emergence of new ontologies (models of entities and relationships within a domain) in glomerular disease [13]. It is reasonable to fully expect a significant reordering of the current classification of GN. It seems quite likely that this evolution will blur or even eliminate the current primary versus secondary dichotomy of disease classification of GN [14, 15].

Another precision medicine project, the Nephrotic Syndrome Study Network (NEPTUNE), a multisite collaboration, has been actively studying several forms (in reality 'patterns of injury') of GN [minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN)] prospectively since 2010 [16]. Very recently NEPTUNE has added Alport syndrome to its portfolio of 'disease' entities [17]. The NEPTUNE study is complementary to and integrated with the KPMP, but is a stand-alone study. NEPTUNE is funded substantially by the NIH (Rare Disease Clinical Collaboration), NephCure International and the Halpin Foundation and is strongly connected to patient-centered organizations. NEPTUNE is focused on using a systems biology approach to better understand the molecular pathways involved in GN, including nephrotic syndrome [18]. This approach involves gene expression (transcriptomics) of specially processed kidney biopsy tissue, next-generation image analysis and other 'multi-omic' techniques to unravel and interconnect critical pathways in glomerular disease evolution, such as the development of interstitial fibrosis or glomerulosclerosis [19]. Already several key pathways have been identified. Novel programs have been developed to help ensure that patients expressing a particular signature of a molecular pathway (e.g. tumor necrosis factor-α) are linked to clinical trials involving drugs that impact the posited pathogenic cascade (the NEPTUNE–MATCH Program) [20]. Advancing from whole tissue or glomerular-specific messenger RNA characterization, single-cell transcriptomics show great promise in accelerating the search for drugable targets in glomerular diseases [21, 22].

Another multisite collaborative, prospective observational study, CureGN, is designed to foster translation of phenotyping of baseline characteristics of patients with minimal change disease, FSGS, MN and immunoglobulin A nephropathy (IgAN) linked to outcomes [23]. The Digital Pathology Repository (DPR) component of this study and the KPMP will permit the identification of potential novel morphologic parameters that might have utility in creating precision medicine pathways for the treatment of GN, although specific randomized controlled trials (RCTs) are not a fundamental part of the CureGN and KPMP organizational structure [24]. Finally, the National Kidney Foundation (USA) has announced its intent to develop a national registry of patients' kidney diseases in order to foster the aims of precision medicine (www.NKFPatientNetwork.org).

Taken together, these ambitious initiatives and the ancillary studies they have generated show great promise in moving the field of therapeutics in kidney disease, including GN, toward a precision medicine 'modus operandi'. However, only a few changes in how we treat patients with glomerular disease today can be traced to findings in this branch of research. Perhaps none should be expected so soon, as the methods are complex, the pathways innumerable and extensively interactive. A focus on novel therapies directed at a single molecular target may prove to be insufficient and a multi-target approach may be required. The large data generated from such studies demand high-level computational accessibility (e.g. informatics, AI, ML). These sophisticated analytical tools demand careful attention to the potential pitfalls of applying them to biological data, such as genomics [25]. Extensive (global) collaboration is called for in order to ensure appropriate ancestral diversity and sample sizes for inferring meaningful conclusions and creating testable hypotheses concerning treatment effects [26].
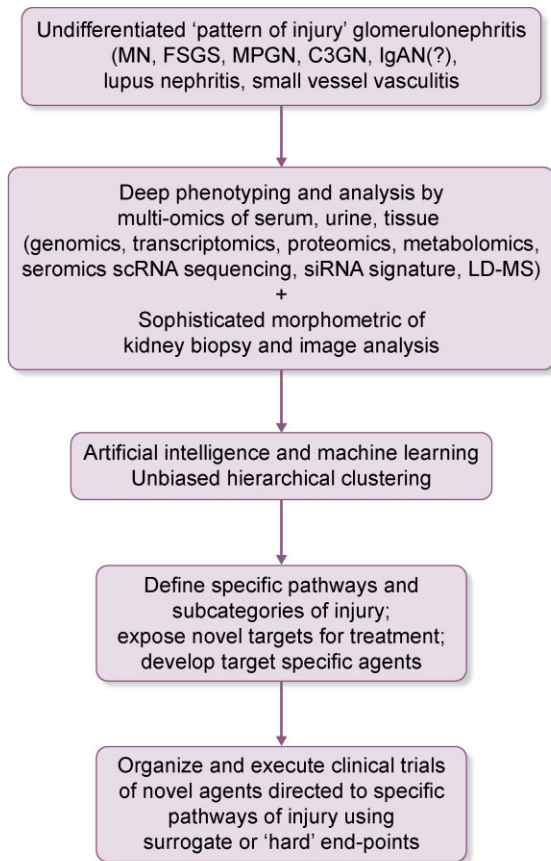
MN = Membranous nephropathy; FSGS = focal and segmental glomerulosclerosis; MPGN = membranoproliferative glomerulonephritis; C3GN = C3 glomerulonephritis; IgAN = IgA nephropathy; scRNA = single cell ribonucleic acid; LD-MS = laser dissection-mass spectrometry

FIGURE 1: A simplified pathway for precision medicine in GN.

The quality control issues surrounding a multi-omics approach to recategorization of GN are formidable but are being addressed prospectively in a rigorous manner [26]. The current pace of discovery emboldens an optimistic assessment of the future for these initiatives. A simplified schema for how precision medicine based on the strategies mentioned above will utilize a pathway of discovery and testing is given in Figure 1.

DEEP PHENOTYPING/GENOTYPING OF PATIENTS WITH GN

While the studies mentioned above will provide crucial insight into the application of precision medicine in glomerular disease, many advances in individualized therapeutic interventions have been made through smaller studies focused on specific diseases or 'patterns of injury'. Deep phenotyping of patients based on urinary or serum biomarkers (such as urinary proteomics or serology) on deep molecular probing of tissue (transcriptomics, single-cell RNA sequencing, laser dissection/mass spectrometry) has shown very promising results. The prospects of a 'liquid' biopsy replacing the standard kidney biopsy have been realized in a few instances [27, 28]. A few of the forms of GN where precision medicine is beginning to have an impact on diagnosis and treatment are discussed below.

MN

The lesion of MN has evolved from a specific disease diagnosis to a less-precise 'pattern of injury' category as a result of defining specific antigen/antibody systems operating in disease pathogenesis via laser dissection–mass spectrometry methodology [29–31]. One 'disease' has become many 'diseases', each having particular clinical features, prognosis and perhaps therapy. The identification of primary versus secondary MN has been irreversibly blurred [14]. Serologic studies detecting and quantifying autoantibody responses (particularly anti-phospholipase A2 receptor antibodies) have now redefined the importance of immunological remission compared with clinical responsiveness (continuum of proteinuria reduction) in defining treatment targets associated with better outcomes [31]. The addition of genomics to the autoantibody profiling of individual patients may also be an emerging paradigm in the diagnosis and treatment of MN [32].

Membranoproliferative GN

The lesion of membranoproliferative GN (MPGN) observed by light microscopy has undergone a similar sequence of being 'downgraded' from a diagnostic term to a pattern of injury that can be evoked by a panorama of pathogeneses [33]. C3 glomerulopathy has emerged as a distinct phenotype, but this lesion is quite heterogeneous in its pathologic pattern and underlying pathogenesis. The complement dysregulation forms of the MPGN lesion have generated widespread interest in complement inhibition as a precision medicine intervention strategy [34]. Early results have been encouraging from the perspective of efficacy and safety [35], but much more needs to be accomplished in order to fully realize the potential of interventions of specific components of the complement cascade (classical, lectin and alternate). There is little doubt that deep phenotyping of the MPGN pattern of injury lesion has brought with it better precision in therapeutic strategies. Unbiased hierarchical clustering analysis of multiple data sources can also generate possible new approaches to therapy [36]. Adding genomic data can even further refine the categorization of disease entities within the rather crude analysis of pathologic findings [37].

IgAN

Much progress has been made in defining the pathogenesis of this common form of GN [38]. A 'four-hit' pathogenic sequence is now fairly firmly established in primary IgAN [39]. Clinical trial design has now incorporated directed therapy to one or more 'hits', but we still fall considerably short of having a well-established precision-based treatment for IgAN-based pathogenesis. Current treatments, such as steroids and/or sodium–glucose cotransporter-2 (SGLT2) inhibitors, lack biomarkers that efficiently predict response in order to facilitate precision medicine [40, 41]. While prognostic scoring systems using clinical features and pathology (Oxford MEST scores) are well established, their role in the selection of patients for specific treatment regimens is highly uncertain [42]. AI methods may even further refine the predictive accuracy for outcomes, such as kidney failure [43]; however, applying these tools to examine the differential efficacy of therapeutic regimens to alter the predicted trajectory is still needed. Perhaps one or more of the trials in progress will fill this gap. Complement inhibition strategies (Hit 4), immune-modulatory drugs focused on B cells (Hits 1 and 2), anti-inflammatory agents (Hit 4) and hemodynamically active

agents (Hit 4) all appear very promising, based on completed or in-progress trials. Novel approaches and biomarkers are sorely needed in IgAN to better delineate the prospects for precision medicine [44]. A preliminary study has suggested that evaluating CD206$^+$ macrophage infiltration in glomeruli might fulfill this role [45].

A large multicenter prospective study is under way to examine the effect of personalized treatment of IgAN with steroids, SGLT2 inhibitors and renin–angiotensin inhibitors (NCT04662723). This trial expects to complete the primary phase by July 2024 [46]. The very impressive findings of a large genome-wide association study (GWAS) involving 38 897 individuals (10 146 with IgAN and 28 751 controls) that identified 30 independent risk loci (16 novel and 14 known), each of which might represent a drugable target, provide much optimism concerning the utility of polygenic risk scoring and deep phenotyping as a route to precision medicine in IgAN [47]. The 'big' data nature of these studies also invokes the powerful tools of AI and ML for unraveling the complexity of the genome-treatment axis. However, rigorous attention to the details of analytic processes will be required [25]. These GWAS discoveries also raise a new long-standing question as to whether IgAN, as it has been historically phenotypically described, represents just a single disease or many different diseases. Nevertheless, the convergence of sets of inflammatory signaling pathways, mucosal immunity and cytokine engagement pathways elucidates a framework for novel agent development and a movement toward precision medicine in IgAN, similar to the events occurring in medical oncology [47].

FSGS

The pattern of injury lesion of FSGS is the best example of how deep phenotyping can lead to precision diagnosis and treatment. Among the glomerulonephritides, it is the poster child for the potential of tangible benefits of a precision medicine approach. The light microscopic lesion of FSGS is very heterogeneous in both pathology and pathogenesis and is not a logical target *per se* for treatment. We now clearly understand that this lesion requires a cause-specific management strategy [48]. This is a model of how precision medicine can be practiced to the benefit of patients, avoiding useless treatment and employing effective and available therapies judiciously. The next step will be to develop and test agents, in suitably designed RCTs, targeted to the unique pathogenesis of FSGS in the individual patient. The definition of categories of the FSGS lesion [primary (presumed permeability factor related), genetic, secondary and unknown] is crucial to the rational design of clinical trial strategies for finding safe and effective treatment modalities [48]. Such strategies are already in progress. Nevertheless, a large gap exists in the precision medicine approaches to an FSGS lesion. The lack of a reliable and accurate biomarker for definition of primary (permeability factor related) FSGS is a major stumbling block [49]. Perhaps the multi-omics approach using kidney tissue or urine will help to identify new target pathways. Preliminary findings from the NEPTUNE study and others are encouraging [50–52]; however, the results of clinical trials of therapy on pathways defined by bulk or single-cell transcriptomic signatures will be needed to confirm the value of this approach.

Lupus nephritis (LN) and vasculitis

Precision medicine has made few inroads in the management of LN. Yes, kidney biopsy and the application of classification of morphological categories are commonly used to make decisions concerning the type of immunosuppression utilized [53]. How-

ever, this is a rather crude and not entirely dependable approach. Molecular probing of pathways involved in the generation of LN patterns of injury is in a developmental phase and much needs to be accomplished before a truly precision medicine paradigm can be applied in the very heterogeneous disorder covered by the blanket term of LN [54]. Preliminary findings of genetic loci responsible for heterogeneity of systemic lupus erythematosus and LN among ancestral groups are a promising avenue of research [55]. Perhaps a polygenic risk score for LN will emerge from these pioneering studies, thus facilitating the design of therapeutic trials based on genetic determinants of risk rather than pathology or clinical variables, similar to that being described in IgAN [55].

Systemic and renal-limited vasculitis has been a bit more successful than LN in engaging a precision medicine approach to therapy. The serology of such vasculitides, anti-proteinase 3 versus anti-myeloperoxidase, seems to be linked to the efficacy of common therapeutic agents, such as rituximab or cyclophosphamide, for initial therapy and long-term avoidance of relapses [56–58]. Serological classification of the vasculitic disorders holds promise in providing tools for precision medicine in diagnosis and management. The recognition that complement activation plays a vital role in the inflammatory component of small vessel vasculitis has led to a highly encouraging advance in the therapeutic armamentarium available in these disorders [59–62].

A WAY FORWARD

The route to an era of precision medicine for all has many alternate versions. No single path can yet be identified that will allow us to reach this goal most expeditiously and economically. Very clearly, at least to me, reaching this utopian goal will be fraught with obstacles that must, and can, be overcome. First, it will require a strong commitment to universal collaboration, across geopolitical boundaries, to ensure that the extraordinary diversity of *Homo sapiens* is accounted for in the designed studies involving humans. Second, engagement with patients, both real and expected, and their families will be necessary to ensure that hopes, wishes, desires and risk tolerance of the affected patients are incorporated into the structure of the research effort. In the end, the realization of precision medicine as a viable and evidence-based practice enterprise will require that the patients willingly and in a well-informed way volunteer for participation in the required RCTs implicit to the full realization of the defined goal. Third, investment of funds supporting the needed infrastructure (computational, imaging and molecular) for the research enabling precision medicine must be sufficient and a long-term commitment to support these very promising initiatives will be absolutely necessary. Fourth, a synergistic, well-structured collaborative effort between consortia of precision medicine investigators and the pharmaceutical industry will facilitate the translation of new discoveries into practical reality. Fulfillment of these perceived requirements seems achievable and already many of the precision medicine projects have incorporated these principles. Eventually the overall cost-effectiveness of a precision medicine approach will have to be critically examined and ways will have to be found to bring these advances to high-, middle- and low-income countries in an equitable fashion. All in all, the future appears bright, but the road ahead will be challenging. Whatever path is taken, the trip is a worthy one and many future patients are likely to experience the benefits of an individualized rather than a one size-fits-all treatment of their disease.

FUNDING

CONFLICT OF INTEREST STATEMENT

The author is a compensated Consultant to: ChemoCentryx, Omeros, Ionis, Travere, Horizon Pharma, BioCryst, Equillium, Aurinia, Calliditas, RenaSight (Natera), Novartis, River3Renal, Vertex, Forsee Pharma, Otsuka, Anteris, Therini, Nephro-Sys, Arrowhead, Alexion, Chinook and National Institutes of Health. He also receives stipend for Editorial services from Wolters-Kluwer (UpToDate) and Karger Publications (American Journal of Nephrology and Nephrology Viewpoints).

REFERENCES

1. Janiaud P, Serghiou S, Ioannidis JPA. New clinical trial designs in the era of precision medicine: an overview of definitions, strengths, weaknesses, and current use in oncology. *Cancer Treat Rev* 2019; 73: 20–30

2. Sethi S. Membranous nephropathy: a single disease or a pattern of injury resulting from different diseases. *Clin Kidney J* 2021; 14: 2166–2169

3. Obama B. *State of the Union Address*. US Congress. January 20, 2015. obamawhitehouse.archives.com (31 December 2021, date last accessed)

4. Boulton F. Blood transfusion and the World Wars. *Med Confl Surviv* 2015; 31: 57–68

5. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015; 372: 793–795

6. 100,000 Genomes Project Pilot Investigators. 100,000 genomes pilot on rare-disease diagnosis in health care—preliminary report. *N Engl J Med* 2021; 385: 1868–1880

7. *Heirarchical Clusterings*. wikipedia.com (31 December 2021, date last accessed)

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

9. Brown KD, Campbell C, Roberts GV. Precision medicine in kidney disease: the patient's view. *Nat Rev Nephrol* 2020; 16: 625–627

10. Tuttle KR, Knight R, Appelbaum PS *et al*. Integrating patient priorities with science by community engagement in the kidney precision medicine project. *Clin J Am Soc Nephrol* 2021; 16: 660–668

11. Poggio ED, McClelland RL, Blank KN *et al*. Systematic review and meta-analysis of native kidney biopsy complications. *Clin J Am Soc Nephrol* 2020; 15: 1595–1602

12. Ong E, Wang LL, Schaub J *et al*. Modelling kidney disease using ontology: insights from the kidney precision medicine project. *Nat Rev Nephrol* 2020; 16: 686–696

13. Niel O, Bastard P. Artificial intelligence in nephrology: core concepts, clinical applications, and perspectives. *Am J Kidney Dis* 2019; 74: 803–810

14. Glassock RJ. Membranous nephropathy: classification redux. *Mayo Clin Proc* 2021; 96: 523–525

15. Bobart SA, Tehranian S, Sethi S *et al*. A target antigen-based approach to the classification of membranous nephropathy. *Mayo Clin Proc* 2021; 96: 577–591

16. Gadegbeku CA, Gipson DS, Holzman LB *et al*. Design of the Nephrotic Syndrome Study Network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach. *Kidney Int* 2013; 83: 749–756

17. Mitrofanova A, Molina J, Varona Santos J *et al*. Hydroxypropyl-β-cyclodextrin protects from kidney disease in experimental Alport syndrome and focal segmental glomerulosclerosis. *Kidney Int* 2018; 94: 1151–1159

18. Schaub JA, Hamidi H, Subramanian L *et al*. Systems biology and kidney disease. *Clin J Am Soc Nephrol* 2020; 15: 695–703

19. Eddy S, Mariani LH, Kretzler M. Integrated multi-omics approaches to improve classification of chronic kidney disease. *Nat Rev Nephrol* 2020; 16: 657–668

20. Kretzler M. NEPTUNE–MATCH program. NCT04571658. https://www.clinicaltrials.gov/ct2/show/NCT04571658? term=04571658&draw=2&rank=1 (16 January 2022, date last accessed)

21. Miao Z, Humphreys BD, McMahon AP *et al*. Multi-omics integration in the age of million single-cell data. *Nat Rev Nephrol* 2021; 17: 710–724

22. Wu H, Humphreys BD. The promise of single-cell RNA sequencing for kidney disease investigation. *Kidney Int* 2017; 92: 1334–1342

23. Mariani LH, Bomback AS, Canetta PA *et al*. CureGN study rationale, design, and methods: establishing a large prospective observational study of glomerular disease. *Am J Kidney Dis* 2019; 73: 218–229

24. El-Achkar TM, Eadon MT, Menon R *et al*. A multimodal and integrated approach to interrogate human kidney biopsies with rigor and reproducibility: guidelines from the Kidney Precision Medicine Project. *Physiol Genomics* 2021; 53: 1–11

25. Whalen S, Schreiber J, Noble WS *et al*. Navigating the pitfalls of applying machine learning in genomics. *Nat Rev Genet* 2021; doi: 10.1038/s41576-021-00434-9

26. Tarazona S, Balzano-Nogueira L, Gómez-Cabrero D *et al*. Harmonization of quality metrics and power calculation in multi-omic studies. *Nat Commun* 2020; 11: 3092

27. Latosinska A, Siwy J, Faguer S *et al*. Value of urine peptides in assessing kidney and cardiovascular disease. *Proteomics Clin Appl* 2021; 15: e2000027

28. Bobart SA, Han H, Tehranian S *et al*. Noninvasive diagnosis of PLA2R-associated membranous nephropathy: a validation study. *Clin J Am Soc Nephrol* 2021; 16: 1833–1839

29. Alsharhan L, Beck LH Jr. Membranous nephropathy: core curriculum 2021. *Am J Kidney Dis* 2021; 77: 440–453

30. Sethi S. New 'antigens' in membranous nephropathy. *J Am Soc Nephrol* 2021; 32: 268–278

31. Ronco P, Beck L, Debiec H *et al*. Membranous nephropathy. *Nat Rev Dis Primers* 2021; 7: 69

32. Xie J, Liu L, Mladkova N *et al*. The genetic architecture of membranous nephropathy and its potential to improve non-invasive diagnosis. *Nat Commun* 2020; 11: 1600

33. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. *Semin Nephrol* 2011; 31: 341–348

34. Smith RJH, Appel GB, Blom AM *et al*. C3 glomerulopathy—understanding a rare complement-driven renal disease. *Nat Rev Nephrol* 2019; 15: 129–143

35. Ort M, Dingemanse J, van den Anker J *et al*. Treatment of rare inflammatory kidney diseases: drugs targeting the terminal complement pathway. *Front Immunol* 2020; 11: 599417

36. Iatropoulos P, Daina E, Curreri M *et al*. Cluster analysis identifies distinct pathogenetic patterns in C3 glomerulopathies/immune complex-mediated membranoproliferative GN. *J Am Soc Nephrol* 2018; 29: 283–294

37. Ahmad SB, Bomback AS. C3 glomerulopathy: pathogenesis and treatment. *Adv Chronic Kidney Dis* 2020; 27: 104–110

38. Knoppova B, Reily C, King RG *et al*. Pathogenesis of IgA nephropathy: current understanding and implications for development of disease-specific treatment. *J Clin Med* 2021; 10: 4501

39. Suzuki H, Kiryluk K, Novak J *et al*. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol* 2011; 22: 1795–1803

40. Lv J, Zhang H, Wong MG *et al*. Effect of oral methyl-prednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA* 2017; 318: 432–442

41. Wheeler DC, Toto RD, Stefánsson BV *et al*. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int* 2021; 100: 215–224

42. Rovin BH, Adler SG, Barratt J *et al*. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int* 2021; 100: 753–779

43. Bülow RD, Dimitrov D, Boor P *et al*. How will artificial intelligence and bioinformatics change our understanding of IgA nephropathy in the next decade? *Semin Immunopathol* 2021; 43: 739–752

44. Hilhorst M, Anders HJ. IgA nephropathy needs a diagnostic marker of immunologic activity to select the right patients for immunotherapies. *J Am Soc Nephrol* 2021; 32: 2982–2984

45. Xie D, Zhao H, Xu X *et al*. Intensity of macrophage infiltration in glomeruli predicts response to immunosuppressive therapy in patients with IgA nephropathy. *J Am Soc Nephrol* 2021; 32: 3187–3196

46. Schena FP, Anelli VW, Trotta J *et al*. Development and testing of an artificial intelligence tool for predicting end-stage kidney disease in patients with immunoglobulin a nephropathy. *Kidney Int* 2021; 99: 1179–1188

47. Kiryluk K, Sanchez-Rodriguez E, Zhou Xu-J. GWAS defines pathogenic signaling pathways and prioritizes drug targets for IgA nephropathy. *medRxiv* 2021; https://doi.org/10.1101/2021.11.19.21265383

48. De Vriese AS, Wetzels JF, Glassock RJ *et al*. Therapeutic trials in adult FSGS: lessons learned and the road forward. *Nat Rev Nephrol* 2021; 17: 619–630

49. den Braanker DJW, Maas RJ, Deegens JK *et al*. Novel in vitro assays to detect circulating permeability factor(s) in idiopathic focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2021; 36: 247–256

50. Chung CF, Kitzler T, Kachurina N *et al*. Intrinsic tumor necrosis factor-α pathway is activated in a subset of patients with focal segmental glomerulosclerosis. *PLoS One* 2019; 14: e0216426

51. Menon R, Otto EA, Hoover P *et al*. Single cell transcriptomics identifies focal segmental glomerulosclerosis remission endothelial biomarker. *JCI Insight* 2020; 5: e133267

52. Latt KZ, Heymann J, Jessee JH *et al*. Urine single-cell RNA sequencing in focal segmental glomerulosclerosis reveals inflammatory signatures. *Kidney Int Rep* 2021; doi: 10.1016/j.ekir.2021.11.005

53. Anders HJ, Saxena R, Zhao MH *et al*. Lupus nephritis. *Nat Rev Dis Primers* 2020; 6: 7

54. Almaani S, Prokopec SD, Zhang J *et al*. Rethinking lupus nephritis classification on a molecular level. *J Clin Med* 2019; 8: 1524

55. Wang YF, Zhang Y, Lin Z *et al*. Identification of 38 novel loci for systemic lupus erythematosus and genetic heterogeneity between ancestral groups. *Nat Commun* 2021; 12: 772

56. Kitching AR, Anders HJ, Basu N *et al*. ANCA-associated vasculitis. *Nat Rev Dis Primers* 2020; 6: 71

57. Segelmark M. Serological testing in small vessel vasculitis. *Rheumatology (Oxford)* 2020; 59: iii51–iii54

58. Thompson GE, Fussner LA, Hummel AM *et al*. Clinical utility of serial measurements of antineutrophil cytoplasmic antibodies targeting proteinase 3 in ANCA-associated vasculitis. *Front Immunol* 2020; 11: 2053

59. Trivioli G, Vaglio A. The rise of complement in ANCA-associated vasculitis: from marginal player to target of modern therapy. *Clin Exp Immunol* 2020; 202: 403–406

60. Zipfel PF, Wiech T, Rudnick R *et al*. Complement inhibitors in clinical trials for glomerular diseases. *Front Immunol* 2019; 10: 2166

61. Jayne DRW. Complement inhibition in ANCA vasculitis. *Nephrol Ther* 2019; 15: 409–412

62. Jayne DRW, Merkel PA, Schall TJ *et al*. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021; 384: 599–609