kidney is not enough to induce recurrent disease—more than genetic risk is needed. The study of Sadowski et al., reporting that a single gene causes steroid-resistant nephrotic syndrome in 30% of children and young adults, owns its success to the fact that patients had an excellent ‘marker’ for a genetic disease: a positive family history. However, mutations in adult patients without family history are extremely rare and screening is not recommended.

We agree with Doctors Mariani and Kretzler regarding the ‘paucity of robust data from RTC to support treatment recommendations’ in glomerular diseases. However, this is in great part due to the lack of interest from the funding agencies in conducting translational research. Instead, significant funding is invested in sophisticated research far away from the bedside, thus delaying clinician access to therapeutical approaches that could help patients today.

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Moderator’s view: Biomarkers in glomerular diseases—translated into patient care or lost in translation?

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A biomarker is defined as ‘A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention’ [1]. Characteristics of an ideal biomarker are indicated in Table 1 [2, 3]. In the field of renal function and renal diseases, urinary protein excretion, urinary sediment, serum creatinine and estimated glomerular filtration rate (eGFR) are commonly used parameters that fulfill the definition of a biomarker. However, they lack both specificity and sensitivity. For instance, persistence of low-grade proteinuria in membranous nephropathy or systemic lupus erythematosus (SLE) may result from still active disease or scar lesions that imply a different therapeutic strategy. Measurement of total proteinuria does not tell us about its composition, and the respective part of glomerular proteinuria made of albumin and high-molecular weight (HMW) proteins (in the case of severe alteration of the glomerular filter) and of tubular proteinuria, made of low-molecular weight proteins, which is an ominous prognostic factor in most glomerular diseases [4–6]. Serum creatinine levels start to rise only when a substantial part, >50%, of the nephrons have been destroyed. eGFR is more sensitive than creatinine but yet, lags far behind renal lesions.

Therefore, there is an urgent need for more sensitive and specific biomarkers of glomerular diseases with the aim of detecting early onset, predicting outcome, monitoring disease activity and adapting therapies. Such biomarkers are eagerly awaited in randomized clinical trials where it is no longer possible to rely on hard end points such as remission of nephrotic syndrome in chronic glomerulopathies or end-stage renal disease (ESRD), which calls for surrogate, reliable biomarkers. For instance, in patients with membranous nephropathy, a proteinuria end point at 12 months may be too soon to evaluate the true effect of treatment as mentioned by Fervenza and De Vriese [7], and some authors argue that this end point should not be earlier than 18 months from the start of treatment, that is 2 years from the diagnosis as an average [8].

In the past decade, a growing number of publications have been devoted to novel biomarkers of glomerular diseases. These biomarkers are the fruits of the substantial advances that have occurred in the understanding of the pathomechanisms of immune-mediated glomerulonephritis. But what has really been achieved that can be translated in practical terms for the pathologists, the clinicians and more importantly for the patients? Where do the advances modify diagnostic tests and classification of diseases leading to a new ontology? What
is the impact on therapeutic strategies? What are the hopes and what are the threats? These questions have been addressed by the two debaters who present two faces of the coin. On the one side, Fervenza and De Vries have taken the example of three glomerular diseases where the contribution of novel biomarkers has as yet been marginal. The first is focal segmental glomerulosclerosis (FSGS) where the nature of the putative circulating permeability factor(s) is still elusive despite some clues provided by works on podocyte-secreted angiopoietin-like 4 [9] and on the more controversial suPAR, the soluble urokinase-type plasminogen activator receptor [10]. Recent data indicate that abatacept, a costimulatory inhibitor that targets CD80/B7-1, might be efficient in some B7-1-positive proteinuric diseases particularly FSGS [11], although these data led to controversial comments and will need independent confirmation. Actually, FSGS is a lesion, not a syndrome, which most likely explains the lack of convincing data collected in a heterogeneous population of patients. I agree with Fervenza and De Vries that a major flaw of many of these studies is the lack of precise clinical evaluation and electron microscopy data, making it difficult to categorize the patients as having an active or inactive disease and even more, a primary or secondary form of FSGS. The second disease is diabetic nephropathy where one dramatically lacks markers of glomerular damage despite a wealth of candidates [12]. Fervenza and De Vries make the point that one should optimize control of the traditional risk factors and invest in patient education rather than in biomarker discovery. This statement is indeed sound in terms of healthcare budget, although it should not detract from further research and even more importantly from testing these novel biomarkers in deeply phenotyped patients. As appropriately pointed out, discrepancies between severity of histological lesions and renal function as assessed by microalbuminuria, proteinuria and eGFR are not uncommon in diabetic nephropathy, which should lead to performing a kidney biopsy as part of the deep phenotyping of the patients. The same holds true for SLE where novel biomarkers do not perform better than proteinuria or urinary sediment. A major potential benefit of biomarkers would be to non-invasively determine which class of lupus nephropathy is present in the patient and whether renal lesions are active or fibrotic. The presence of dysmorphic red blood cells suggests an active class III or IV nephritis while heavy proteinuria is more suggestive of membranous nephropathy. Although some data suggest that a combination of biomarkers is associated with histological features of lupus nephritis [13], none of these tests are reliable enough to take the place of a kidney biopsy for the diagnosis of renal lesions and the evaluation of treatment efficacy.

On the other side, Mariani and Kretzler [14] advocate for more personalized medicine relying on a better definition of diseases and precise appreciation of personal risk based on a combination of genetic, epigenetic, urine and serum protein, and pathology and morphometric biomarkers. This approach is needed because of pathological and clinical heterogeneity of glomerular diseases. For instance, IgA nephropathy has heterogeneous clinical and pathological presentation, and a variable, somewhat unpredictable outcome. It has now become clear that the patients coming to clinical attention are only the tip of the iceberg [15]. Heterogeneity of IgA nephropathy is well reflected by the many loci that were identified in pangenomic studies while only two loci, HLADQA1 and PLAR2, showed up in similar studies of Caucasian patients with idiopathic membranous nephropathy [16]. But even in the latter glomerulopathy, outcome is quite unpredictable with 40% of the patients entering spontaneous remission while 30% will advance to ESRD. Among the genetic, proteomic and morphometric biomarkers discussed by Mariani and Kretzler, anti-PLAR2 antibodies detected in adult patients with membranous nephropathy can be considered as ideal biomarkers, because they have diagnostic, prognostic and predictive values [17, 18]. Actually, they fulfill all the criteria mentioned in Table 1. They are easily measured in the serum by affordable tests (in the industrialized countries) based on immunofluorescence and ELISA, both approved by the Food and Drug Administration and the European Medicines Agency. Their specificity for membranous nephropathy is close to 100%. Their sensitivity comprised between 70 and 80%. A growing body of evidence suggests that high titres of PLAR2 antibodies are associated with a lower rate of spontaneous remission, a higher risk of occurrence of overt nephrotic syndrome in the non-nephrotic patients and of deterioration of renal function, and a lower rate of immunological remission in patients treated with rituximab. Furthermore, treatment-induced antibody depletion is a strong predictor of clinical remission occurring several weeks or months after immunological remission while reappearance, or increasing titres, of antibodies is predictive of relapse [19]. These findings have led to the concept of immunological remission, defined by antibody depletion, preceding clinical remission, defined by proteinuria. They already have a major impact on the timing and monitoring of immunosuppressive treatment. They should pave the way for similar approaches in other glomerular diseases.

Are the points of view of our debaters opposite or complementary? Fervenza and De Vries strongly defend a meticulous clinical approach, somewhat anachronistic in a medical world where careful anamnesis and clinical examination tend to be replaced by unthinking, automatic prescription of ultrasound and CT-scan imaging techniques. This clinical approach which is part of the deep phenotyping of patients lays the ground for validation of new biomarkers that can only be achieved in well-defined cohorts of patients. Except for anti-PLAR2 antibodies, the renal community has failed in delivering novel biomarkers, because renal diseases are rare, cohorts of renal patients have only been recently established, and careful patient

### Table 1. Characteristics of an ideal biomarker

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<tr>
<td>1</td>
<td>Non-invasive, easily measured, inexpensive and provides rapid results</td>
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<td>2</td>
<td>From easily available sources (blood or urine)</td>
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<tr>
<td>3</td>
<td>High sensitivity</td>
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<tr>
<td>4</td>
<td>High specificity</td>
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<tr>
<td>5</td>
<td>Allow early detection of disease and changes in response to treatment</td>
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<tr>
<td>6</td>
<td>Predicts prognosis and allows stratification into categories of risk</td>
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<tr>
<td>7</td>
<td>Biologically plausible—provides information about the mechanisms of disease</td>
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From Ref [2]; adapted from Ref [3].
phenotyping has often been neglected. Mariani and Kretzler are on the same line as Fervenza and De Vries when they call for prospective, standardized data collection such as the Nephrotic Syndrome Study Network (NEPTUNE), CureGN, EurenOomics, Podonet and RADAR [14]. They also admit that the ‘tools guiding future clinical management most likely will continue to include histology, established laboratory parameters and clinical judgment’.

Why do we need novel biomarkers? We need them for improved classification of diseases and more personalized medicine. Once again, membranous nephropathy can be taken as an example. The characterization of anti-PLA2R antibodies has rendered useless the meaningless term of ‘idiopathic’ membranous nephropathy. Patients should now be classified according to serology in PLA2R-positive and PLA2R-negative membranous nephropathy. The PLA2R-negative ones should subsequently be categorized according to the presence or the absence of antibodies to thrombospondin type-1 domain-containing 7A [20]. Although response to rituximab does not differ according to PLA2R serology, those classifications are important because of their impact on prognosis, monitoring and further therapeutic protocols [19]. Oncology is the leading specialty from which lessons should be learnt in term of biomarkers. In cancer therapy, personalized treatment based on an extensive characterization of the tumour cells both in the primary tumour and in the metastases has become the rule [21], and several lines of treatment according to the evolution of markers are proposed. In contrast, treatment of immune-mediated glomerulonephritis has remained very empirical and still relies to a large extent on a single line of non-specific therapies such as corticosteroids and immunosuppressive drugs that are more or less the same since >30 years. The only two notable exceptions are eculizumab and rituximab. It is interesting to note that the latter anti-B cell therapy was initially used in B-cell lymphomas and leukaemias. We are still far from therapies targeting specific mediators at different stages of the nephropathy partly because we still lack reliable biomarkers such as hormonal receptors, growth factor receptors or oncogene rearrangements or mutations.

In a recent editorial related to biomarkers in AKI [22], Bruce Molitoris pointed out that during the past 10 years, ‘tremendous amounts of time, effort and money have been invested to develop clinically useful biomarkers for determination of risk, diagnosis, and prognosis’. However, the quest of the ‘Holy Grail’ has been mostly disappointing. This is the reason why Fervenza and De Vries argue that in diabetic nephropathy, rather than to pursue the search for novel biomarkers, one should invest in patient education, careful follow-up and prevention. This point is well taken if one looks at the return on investment of most part of biomarker research. However, building on the example of PLA2R antibody, the search for biomarkers should also be pursued provided we have ‘the tools and the cohorts of deeply phenotyped patients to start this journey in earnest’ as emphasized by Mariani and Kretzler. We are at the very beginning of a new era in this field where success will crucially depend on meticulous clinical characterization of the patients, rigorous biostatistics and integration of multiple layers of data across the genotype-phenotype continuum of glomerular diseases.

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### CONFLICT OF INTEREST STATEMENT

None declared.


### REFERENCES


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