I predict that biomarkers (in urine or serum) will continue to evolve in sophistication, accuracy, reliability and cost-effectiveness, consequent to efforts described by Mischak et al. [11]. Concurrently, evaluation approaches to renal biopsy tissue will also expand beyond mere histological assessment [12]. However, for the foreseeable future ‘liquid’ biopsy will be complementary to rather than substitutes for ‘needle’ kidney biopsy in many diseases confronted by clinical nephrologists.

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Moderator’s view: Will ‘modern’ urine proteomics replace ‘old-fashioned’ renal biopsy?

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In this Polar View, Richard Glassock [1] concludes that ‘…it is highly unlikely that the surge in biomarker technology development will lead to abandonment of renal biopsy as a useful clinical (and research) tool’. In contrast, Harald Mischak [2], in his response to Richard Glassock, considers a kidney biopsy to be currently unethical and possibly illegal as long as urine proteome and other options have not been exploited and as long as therapy cannot be based on the latter. It is important to keep in mind that Harald Mischak is co-founder and co-owner of Mosaigues Diagnostics GmbH, i.e. a company developing proteomic tests, and thus has a major conflict of interest. So far, I am not aware of any ethics committee decision or legal cases that follow Dr Mischak’s line of arguments, and I strongly disagree with Dr Mischak’s opinion that a renal biopsy is unethical or even illegal.

But rather than getting lost in a debate on opinions, let us have a look at the key arguments of the two opponents and see how they apply to both methods (Table 1).

Other important arguments in favour of a proteomic approach are that it may allow a much earlier detection of disease than a biopsy. I agree, but if correct, I wonder what the implications are. In many instances, early detection of disease is of unknown relevance. A good example is IgA nephropathy, where the vast majority of cases detected very early run a very benign course [3], and where early therapeutic interventions have failed so far to translate into a long-term benefit [4]. In this respect, the PRIORITY study mentioned by Dr Mischak will be of great interest, but data will not be available before 2018. In addition, early detection would call for broad screening. Can we afford this given the cost of proteomic analyses?
However, at least one recent multicentre study demonstrated intuitively I would suspect that proteomic patterns are mainly composed of metabolized and/or degraded renal proteins (mainly collagen), whereas renal biopsies reflect the overall morphology of the kidney, and this might provide a more comprehensive description of the status quo of the kidney than urine proteomics. In addition, urine proteomic profiles might be influenced by comorbidities. Finally, postrenal metabolism and/or degradation of peptides, for example in the bladder, may occur, and further compounds will enter the urine downstream of the kidneys. Thus, it is important to keep in mind that urine proteomic profiles do not selectively mirror the kidneys.

From a technical point of view, a proteomic approach might yield better reproducibility than a kidney biopsy, and this may increase further in the future since urine proteomic tests are automatable, in principle, which will likely improve both reproducibility and costs of the method. Dr Mischak cites a study on the classification of lupus nephritis as class III or IV [5] as evidence that interobserver agreement in the case of a renal biopsy is low. I fully agree that reading a biopsy is more subjective than reading a proteomic profile, and this is why we need experienced and well-trained nephropathologists. In particular, sampling error is not a concern in a proteomic approach since urine integrates all of the kidney proteome, and this might provide all this data in one or several snapshots.

In terms of analytical error, an issue that has not been studied very broadly is the effects of behavioural patterns on proteomic or biopsy findings. What, for example, is the short-term effect of smoking, heavy exercise prior to the test or particular diets on the day of or the day preceding the test, short-term blood pressure changes, etc.? No doubt, this has not been studied systematically in renal biopsies either, but intuitively I would suspect that proteomic profiles in the urine may change much more rapidly than histological patterns. However, at least one recent multicentre study demonstrated that the urine proteomic profiles of CKD patients from different European countries are comparable [7].

A major benefit of a proteomic approach is its non-invasive nature and thus the option to perform it repeatedly with no risk to patients. Dr Mischak states that ‘…it is conceivable that additional studies, linking the urinary proteome to drug response, will enable prediction of drug response based on the urinary proteome’ [8–10]. However, so far the studies raising such hope are based on small numbers of patients and in particular it is not well established whether changes in the proteomic pattern outperform established clinical or laboratory parameters that are currently in use to assess responses to therapy. So why do I agree with Dr Glassock and still like a kidney biopsy? I want to see a biopsy because of the plethora of information within it, such as the diagnosis, the extent of active inflammation or even necrosis, crescents, glomerulosclerosis, tubulointerstitial injury and fibrosis, vascular changes and possibly a classification. All this will go into my assessment of the prognosis and therapeutic decision-making. I am not yet convinced that a single or even repeated proteomic profiles can reliably provide all this data in one or several snapshots.

Nevertheless, I agree with Dr Mischak that proteomics holds promise, in particular in assessing responses to therapy and changes in the prognosis. However, at present most of this is hope rather than fact, and much needs to be done before urine proteomics can become a routine adjunct method to a kidney biopsy.

### CONFLICT OF INTEREST STATEMENT

None declared.

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