Biomarker research to improve clinical outcomes of peritoneal dialysis: consensus of the European Training and Research in Peritoneal Dialysis (EuTRiPD) network

Christoph Aufricht[1], Robert Beelen[2], Matthias Eberl[3], Michel Fischbach[4], Donald Fraser[3], Achim Jörres[5,6], Klaus Kratochwill[7,8], Manuel LópezCabrera[9], Peter Rutherford[10], Claus-Peter Schmitt[11], Nicholas Topley[3] and Janusz Witowski[12]

[1]Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria; [2]VU Medisch Centrum, Amsterdam, The Netherlands; [3]Cardiff University, Cardiff, UK; [4]Universitéde Strasbourg, Strasbourg, France; [5]Department of Nephrology and Medical Intensive Care, Charité University Hospital Campus Virchow-Klinikum, Berlin, Germany; [6]Department of Medicine I, Nephrology, Transplantation & Medical Intensive Care, University Witten/Herdecke, Medical Center Cologne-Merheim, Cologne, Germany; [7]Zytoprotec, Vienna, Austria; [8]Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical University of Vienna, Vienna, Austria; [9]Centro de Biología Molecular Severo Ochoa - Consejo Superior de Investigaciones Científicas, Madrid, Spain; [10]Glyndŵr University, Wrexham, UK; [11]Universitätsklinikum Heidelberg, Heidelberg, Germany; and [12]Department of Pathophysiology, Poznan University of Medical Sciences, Poznan, Poland

Peritoneal dialysis (PD) therapy substantially requires biomarkers as tools to identify patients who are at the highest risk for PD-related complications and to guide personalized interventions that may improve clinical outcome in the individual patient. In this consensus article, members of the European Training and Research in Peritoneal Dialysis Network (EuTRiPD) review the current status of biomarker research in PD and suggest a selection of biomarkers that can be relevant to the care of PD patients and that are directly accessible in PD effluents. Currently used biomarkers such as interleukin-6, interleukin-8, *ex vivo*–stimulated interleukin-6 release, cancer antigen-125, and advanced oxidation protein products that were collected through a Delphi procedure were first triaged for inclusion as surrogate endpoints in a clinical trial. Next, novel biomarkers were selected as promising candidates for proof-of-concept studies and were differentiated into inflammation signatures (including interleukin-17, M_1/M_2 macrophages, and regulatory T cell/T helper 17), mesothelial-to-mesenchymal transition signatures (including microRNA-21 and microRNA-31), and signatures for senescence and inadequate cellular stress responses. Finally, the need for defining pathogen-specific immune fingerprints and phenotype-associated molecular signatures utilizing effluents from the clinical cohorts of PD patients and "omics" technologies and bioinformatics-biostatistics in future joint-research efforts was expressed. Biomarker research in PD offers the potential to develop valuable tools for improving patient management. However, for all biomarkers discussed in this consensus article, the association of biological rationales with relevant clinical outcomes remains to be rigorously validated in adequately powered, prospective, independent clinical studies.

Kidney International (2017) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2017.02.037

KEYWORDS: epithelial–mesenchymal transition; peritonitis; proteomics; renal replacement therapy; surrogate markers; ultrafiltration failure

Peritoneal dialysis (PD) is an effective, home-based type of renal replacement therapy that promotes patient autonomy. A significant proportion of patients who initiate PD have PD-related clinical complications, including peritonitis and peritoneal membrane damage, that may limit the duration of treatment.[1] PD patients are also at a high risk of other serious and life-threatening illnesses, most notably cardiovascular diseases. However, current approaches to patient monitoring are mostly limited to approximating delivered doses of dialysis and to measuring the membrane transport status. Consequently, despite considerable improvements in patient management and overall technique survival, there is a substantial unmet medical requirement for biomarkers as tools to identify patients who are at the highest risk and to guide personalized interventions to improve the individual clinical outcomes of PD.

In the clinical context, a biomarker is a proxy of disease mechanisms, which provides relevant data for decision making regarding the diagnosis and/or therapy of a patient. Another classical definition is as follows: "a characteristic that is objectively measured and evaluated as an indicator of

Correspondence: *Achim Jörres, Department of Medicine I, Nephrology, Transplantation & Medical Intensive Care, University Witten/Herdecke, Medical Center Cologne-Merheim, Ostmerheimer Str. 200, D-51109 Cologne, Germany. E-mail: JoerresA@kliniken-koeln.de*

Received 28 November 2016; revised 16 February 2017; accepted 27 February 2017

normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention."[2] This information may become directly obvious from the molecular processes that reflect the disease status, such as increased inflammatory mediator levels in biological fluids owing to increased production and release from inflamed tissues or local leukocytes. However, biomarker levels may also reflect mere changes of distribution between compartments, such as leakage from intracellular into extracellular or spill over from systemic into local compartments by altered clearance.[3] Accordingly, the identification and interpretation of appropriate biomarkers are not trivial, and the clinical value of attractive biomarker candidates is difficult to predict and requires careful preclinical and clinical validation.[4]

This consensus article focuses on biomarkers that are considered to be relevant to the care of PD patients but are limited to the local peritoneal level, namely biomarkers that are directly accessible in PD effluents. In what clinical circumstances would these biomarkers be of benefit? When used as a risk assessment tool (Figure 1), prognostic peritoneal biomarkers might help to identify patients who are at the highest risk for PD-related complications. For example, biomarkers that reflect the chronicity of peritoneal inflammatory processes might identify patients prone to a progressive loss of membrane function. Similar to sepsis research, biomarkers that reflect depressed immunocompetence might identify increased infectious susceptibility in PD, such as PD-related peritonitis. Thus, monitoring a set of biomarkers that reflects the activity of relevant pathomechanisms might help to guide therapeutic decisions, or after therapeutic interventions, they might enable early discrimination between responder and nonresponder subgroups. The introduction of such predictive biomarkers (Figure 1) will likely facilitate the implementation of stratified medicine into the clinical setting of PD. For example, a high proinflammatory status in a given PD patient might necessitate the introduction of antiinflammatory local therapy by novel PD fluids. However, biomarkers that predict a particularly high risk for PD-related complications might also allow a timely switch to alternate methods of renal replacement in nonresponding patients. Importantly, combinations of these biomarkers may also be used as surrogate parameters for well-defined hard outcomes in the clinical development of novel PD fluids. Such biomarkers are particularly relevant tools because the hard outcomes require large studies with several hundred patients observed over several years and thus present major logistic and economic obstacles for dearly needed early clinical trials in PD.[1] Finally, biomarkers might also be implemented as a diagnostic tool. For example, a certain pattern of cytokines

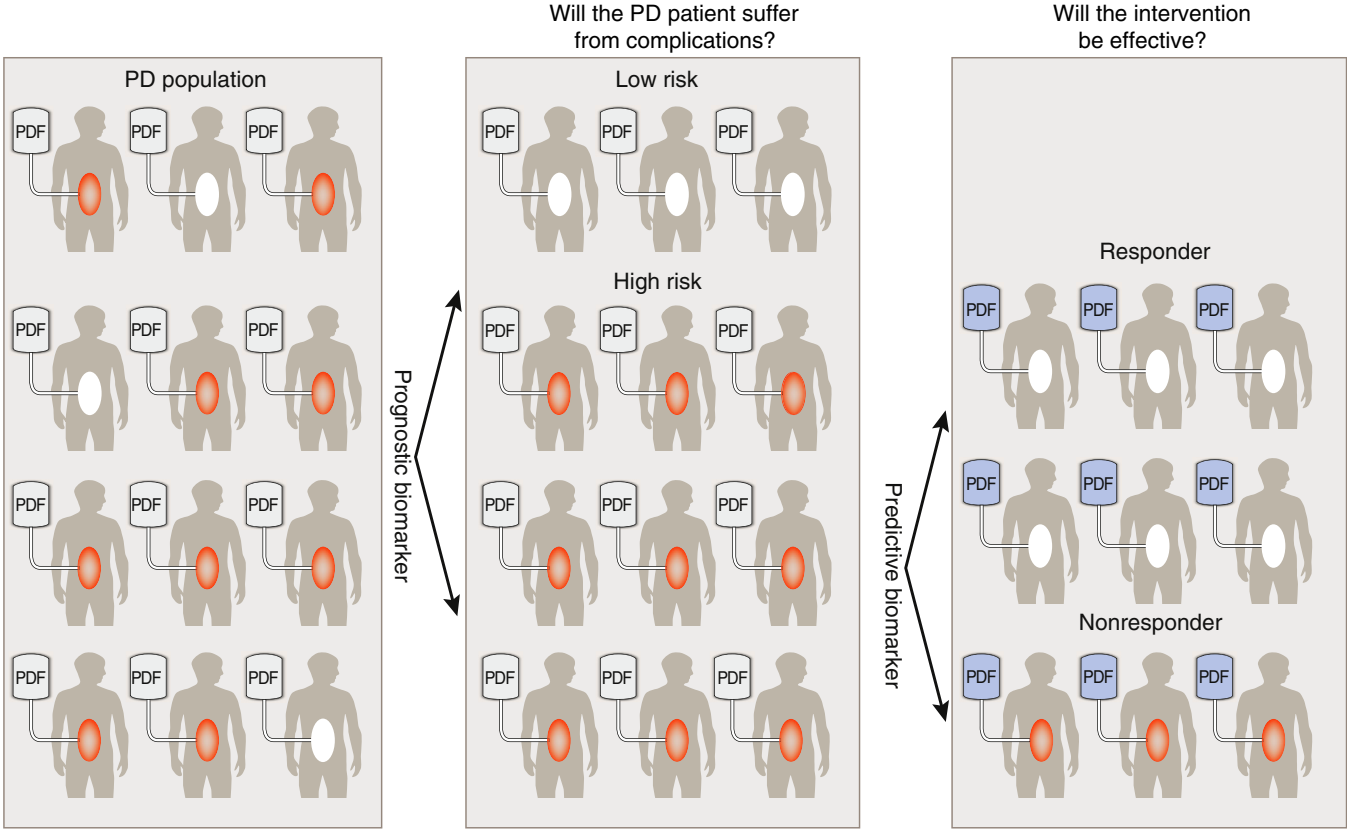

Figure 1 | Prognostic biomarkers help to identify peritoneal dialysis (PD) patients who are at a high risk of complications (such as peritoneal membrane deterioration and peritonitis) and should receive counteracting interventions (such as novel peritoneal dialysis fluids [PDFs]). Predictive biomarkers help to identify those PD patients who are most responsive (or unresponsive) to a given intervention.