Dear editor and reviewers,

Thank you very much for your encouragement and all your suggestions and comments, which we believe have not only increased the quality of our editorial but its reach and utility.

Our editorial has changed significantly. We did many changes throughout the text to improve its clarity, and we added two extra sections at the end, one on immunological risk and one with suggestions and recommendations for biomarker research.

We thank you in advance the time and effort spent in reviewing our revised version, hoping your approval for publication.

Please see below our specific replies to your kind and useful comments and actions taken.

- *This article provided updated information on opportunities and hurdles encountering in discovering biomarkers in kidney transplantation. Excellent for readers in transplantation field. But if guideline recommendations included, it would be more valuable.*

Thank you for your suggestion. We have included a new section and a table in the format of recommendations and suggestions, which could serve as the prototype for future guidelines in biomarkers research.

- *The imperfection of measuring the state of immunosuppression – if such single number is to be found, itself a doubtful concept – underlies the imperfection of immunomodulating (immunosuppressive) treatments in transplantations, including in renal transplantation. Current approach is limited by the somewhat arbitrary practice of ordering renal biopsies and the usual practice or creatinine-based process triggering likely to be replaced in the future. As the Authors rightfully editorialize, the immune system is a complex organ system with multiple detector and effector arms, which we are not able to measure anywhere close to precisely. Somewhat analogous to the concept of the false promise of "renal biomarkers" in acute kidney injury (AKI), the Authors of this excellent editorial*

point out the similar limitations of biomarker-based approaches in renal transplantations. To date, none of the approaches have reliably renal allograft biopsy, as the gold standard to detect rejection (thought DSA seem to have added value to biopsy). It is now well recognized that humoral rejection process(es) are more commonly smoldering than previously appreciated. Failure to recognize compliance failure due to medication side effects, proteinuria are additional limitations of current medical practices (Minimization vs. Tailoring - Where Do We Stand with Personalized Immunosuppression during Renal Transplantation in 2015? World J Transplant. 2015 (Sept);5(3):73-80.). All those practice considerations are essential to individual "tailoring" of therapy (rather, than the old expression of "minimizing" immunomodulating therapy!). To take advantage for what we have currently is more important for practicing clinicians than the relentless pursuit of 1 single "magic bullet" in detecting rejection from serum/urine of renal Tx recipients. But, nonetheless, for the future, the potential remains for a mRNA and proteonomics-based "high-resolution" examination of the kidney biopsy samples, an emerging field in nephrology research. Such broad-based approach may help us to select better "biomarker-profile" from serum samples in the future, as well.

Thank you for your interesting views on biomarker research, which are very similar to ours. We did a series of small/discreet changes throughout the manuscript to be sure we cover all your points. We also included your suggested reference. But more importantly, your comment awoke on us the need to incorporate in our editorial the difficult topic and our views on immunological risk but linking it with our recommendations and suggestions in Table 1 (as commenting on immunological risk deserves itself a full review or editorial).

- *Dear professor: Regarding: Biomarkers and a tailored approach for immune monitoring in kidney transplantation, by Dr. Francisco Salcido-Ochoa and Asst/Prof John Carson Allen Jr. It is well written and covered a very interesting although still not practical as mentioned within this interesting editorial discussion. I agree with the authors concepts. It is a valuable state of art to be published as it is without any modification*

Thank you very much for your encouragement, hoping this revised version obtains your approval too.

- *I recommend to prepare a systematic review on the topic, instead*.

Thank you for the suggestion. A very good traditional review enumerating the most promising biomarkers, plus many others, was just published in WJT (reference 13, Salvadori et al, 2017). It would be very difficult to perform systematic reviews on most of these markers given the variety of molecules tested, study designs, detection technologies used, patient populations and bias in the published studies. That is why in our editorial we go back a little bit, point some common down points in those studies and then suggest how to move forward in biomarker research, using a more standardized approach, including their incorporation in well-designed clinical trials.

Thank you very much,
F Salcido-Ochoa and JC Allen Jr