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Introduction: Precision Medicine in End-Stage Kidney Disease and Personalized Renal Replacement Therapy: Challenges and Unmet Need

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Keywords

Precision medicine; end stage kidney disease; mortality; outcomes; personalized medicine; renal replacement therapy

The prevalence of end-stage kidney disease (ESKD) continues to increase in the United States of America with recent estimates indicating a growth rate of 3–4% annually.(1) Furthermore, the incidence and prevalence of ESKD is on the rise globally given that the high burden of the risk factors for chronic kidney disease (CKD) inclding diabetes and hypertension worldwide.(2) The social, healthcare and economic costs of ESKD are immense as indicated by the fact that, while patients with ESKD make up less than 1% of Medicare patients, the cost of their care accounts for over 5% of the Medicare total budget. (1) In addition to the social and economic impacts of ESKD and despite recent improvements in dialysis therapy, these patients continue to suffer from a disproportionately increased risk of morbidity and mortality. For instance the latest estimates indicate that ESKD patients on maintenance hemodialysis experience an annual mortality rate of approximately 15%, a rate worse than that associated with many cancers(1). Meanwhile, the underlying mechanisms responsible for the latter observations are thought to be diverse with the so called “nontraditional” risk factors playing an important role in the pathogenesis of poor outcomes in this patient population. Furthermore, numerous epidemiologic studies have found paradoxical associations between some traditional risk factors and improved outcomes (3). The latter findings are consistent with the results of large randomized clinical trials which have found that therapies addressing certain traditional risk factors (such as HMG-COA reductase inhibition), do not have a meaningful impact in patients with ESKD (4–6). In fact, multiple large clinical trials using various pharmacologic and therapeutic strategies have failed to provide a clinically proven tool that is effective in improving survival in this patient population (4–8). Whereas there are many factors which contribute to these

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disappointing results, there is mounting evidence that a one-size-fits-all approach is unlikely to be effective in patients with ESKD given the unique and vast nature of risk factors encountered in this patient population. In addition, there appears to be significant heterogeneity in patient outcomes in this condition with race and ethnic background playing a key role in prediction outcomes (9). Moreover, there is evolving evidence that the racial disparities in outcomes are most likely driven by genetic factors which have not been accounted for in other patient populations (10). Henceforth, in order to address the uniquely important risk factors that may be present and likely play a key role in pathogenesis of poor outcomes in a given ESKD patient, it is essential that a personalized strategy tailored for each individual is adopted. Furthermore, it is critical that diagnostic and therapeutic tools are developed which can accurately identify patients at risk for poor outcomes and distinguish those who may benefit from a given therapy from those who may not benefit or be potentially harmed due to adverse effects.

In the past few decades, formulation of medical treatments has relied heavily on randomized clinical trials conducted to determine the effect of a therapy on an “average patient”. As a consequence, treatments which result in a desired outcome in a number of patients large enough to reach a given statistical end point are deemed effective and are recommended to that patient population as a whole. However, it important to note that despite the overall positive findings of a given clinical trial, there are individuals within the study who do not benefit from the therapy being evaluated. Conversely, in a clinical trial which does not disprove the null hypothesis and hence is considered negative, there may be patients who derive a benefit from the therapy being administered. Therefore, this approach results in a large number of patients in whom the impact of a given therapy is discounted due to the inherent limitations of population-based methodologies. The precision medicine initiative was launched in 2015 in order to address these discrepancies and to refocus the efforts of the medical community on the care/outcomes of individual patients. The precision medicine approach takes into account the genetic, environmental, and lifestyle factors and preferences, among others, which are unique to each particular patient thereby recognizing the complexity and diversity of different mechanisms that can be present in individuals with the same condition (11, 12). Through this personalized approach, it is hoped that precision medicine can help better predict which treatments will be most effective in each particular case. In light of the complex nature of underlying mechanisms responsible for pathogenesis of disease and poor outcomes in patients with advanced kidney disease and the disappointing results of the population-based studies, the patient-driven approach advocated by precision medicine holds significant promise and is likely to make a major impact in the care of patients with ESKD. While there is much work that remains to be done in this arena, valuable progress has already been made which can serve as the foundation for future studies in this important and worthy area of research.

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