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Kidney dysfunction requiring dialysis is a heterogeneous syndrome: we should treat it like one

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Purpose of review
Advanced kidney failure requiring dialysis, commonly labeled end-stage kidney disease or chronic kidney disease stage 5D, is a heterogeneous syndrome –a key reason that may explain why: treating advanced kidney dysfunction is challenging and many clinical trials involving patients on dialysis have failed, thus far. Treatment with dialytic techniques – of which maintenance thrice-weekly hemodialysis is most commonly used – is broadly named kidney 'replacement' therapy, a term that casts the perception of a priori abandonment of intrinsic kidney function and subsumes patients into a single, homogeneous group.

Recent findings
Patients with advanced kidney failure necessitating dialytic therapy may have ongoing endogenous kidney function, and differ in their clinical manifestations and needs. Different terminology, for example, kidney dysfunction requiring dialysis (KDRD) with stages of progressive severity could better capture the range of phenotypes of patients who require kidney 'assistance' therapy.

Summary
Classifying patients with KDRD based on objective, quantitative levels of endogenous kidney function, as well as patient-reported symptoms and quality of life, would facilitate hemodialysis prescriptions tailored to level of kidney dysfunction, clinical needs, and personal priorities. Such classification would encourage clinicians to move toward personalized, physiological, and adaptive approach to hemodialysis therapy.

Keywords
end-stage kidney disease, hemodialysis, residual kidney function, staging

INTRODUCTION

In the United States, approximately 0.8 million adults have advanced kidney failure receiving dialysis treatments and the number is projected to double by 2030 [1–3]. Healthcare expenditures for patients on chronic dialytic therapy mount up to $35.9 billion, accounting for 7.2% of the overall Medicare-paid claims in the fee-for-service system event though they constitute 1% of the Medicare population [4]. Notably, the mortality rates in patients treated with dialysis, while modestly improved over the last decade, are alarmingly high, rating at 15–30% in the first 4 months after commencing dialysis and 10–20% annually, exceeding by 20-fold that of age-matched individuals in the general United States population [3,5,6]. Five-year and 10 year-survival probabilities for patients on maintenance hemodialysis are worse than for patients with breast cancer, prostate cancer, and colorectal cancer [7▪]. Large

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KEY POINTS

- End-stage kidney disease (ESKD) is a heterogeneous syndrome, yet its treatment with standard schedules of hemodialysis subsumes patients into a single, homogenous group.
- Replacing the umbrella term of ESKD with a new taxonomy under the name of kidney dysfunction requiring dialysis (KDRD) with stages of ascending severity could promote personalized hemodialysis prescription.
- By categorizing patients with KDRD based on quantitative levels of endogenous kidney function, the hemodialysis prescription can be adjusted corresponding to the KDRD stage.
- Improved phenotypic characterization of KDRD, in both the clinic and in clinical trials, is critical in order to improve outcomes in this increasingly prevalent patient population.

investments in oncology research, relative to nephrology research, have driven the development of precision and immune-oncology therapies, offering hope to millions of patients with cancer [8,9].

Differences in the approach to diagnosis and treatment between patients with advanced kidney failure and those with cancer are conspicuous (Fig. 1). In the oncology field, detailed malignancy subcategorization is central to both cancer diagnosis and treatment. Histopathological diagnosis is a requisite for all malignant tumors; in contrast, kidney biopsy is performed in a minority of patients diagnosed with kidney failure [10]. Discrete genetic, epigenetic, and molecular signatures derived from tissue biopsy among cancer phenotypes underpin patient stratification, which have enabled the delivery of personalized treatment to the cancer patient. In fact, molecular screening systems underpin much of drug discovery in oncology [11]. In contrast, patients diagnosed chronic kidney disease who progress to require dialysis are treated as if they have one disease entity, and in-center thrice-a-week hemodialysis is the ubiquitous approach to treatment [12]. In light of this knowledge gap, several research groups have formed in recent years, with the goal of identifying novel diagnostic and prognostic biomarkers by performing high-throughput genetic, genomic, and epigenetic studies on native kidney biopsies in patients with kidney dysfunction [10,13].

TERMINOLOGY

Although such disease characterization work is in its infancy in nephrology, it is clear that kidney failure does not arise from a single disease entity; it is a collection of different diseases and subtypes of kidney dysfunction. Patients with advanced kidney failure requiring dialysis treatment differ at a multitude of levels including endogenous kidney function (e.g. renal urea clearance, urine output per day); biochemical parameters (e.g. metabolic acid, electrolyte, and bone mineral imbalance); and volume overload. Given the multidimensional nature of this illness, we must change our taxonomy and therapies to recognize the full range of clinical conditions. To achieve this objective, a change in disease terminology to kidney dysfunction requiring dialysis (KDRD)

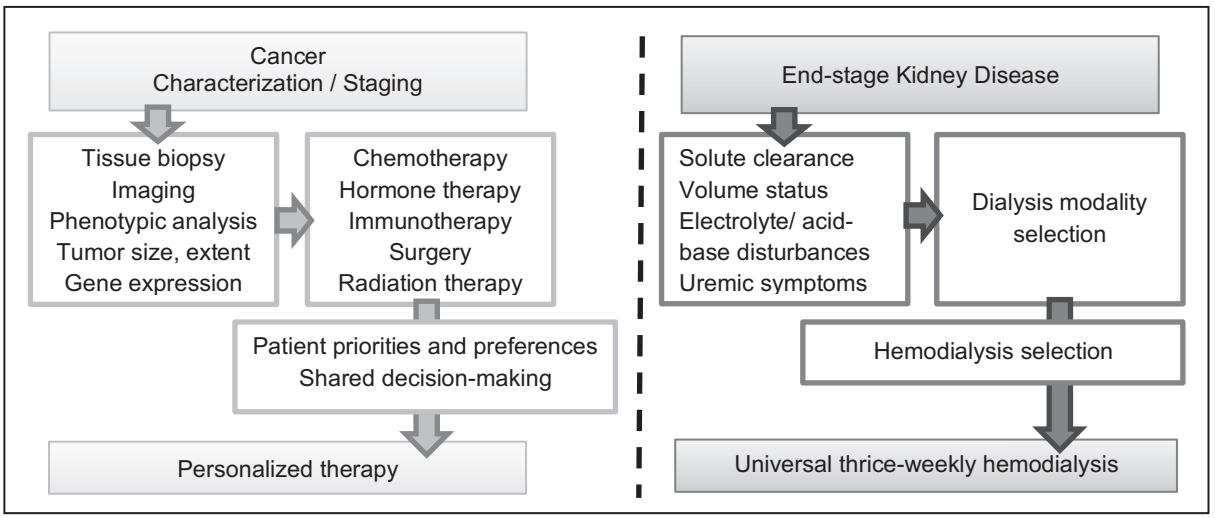

FIGURE 1. Illustration of a targeted treatment approach (e.g. cancer) versus a one-size-fits-all approach (e.g. end-stage kidney disease). Treatment of cancer has benefitted from an increasingly targeted approach whereas thrice-weekly hemodialysis is the mainstay approach to treatment of patients diagnosed with end-stage kidney disease.

with subtypes based on objective, quantifiable criteria, supplemented by patient-reported experiences, might prove more fruitful in guiding individualized therapeutic approaches.

In fact, the Kidney Disease Improving Global Outcomes international organization recently called for refinement of the nomenclature used to describe kidney function and disease [14]. Guiding principles for the revised nomenclature were that it should be patient-centered and precise, with the ultimate goal to facilitate communication within and across disciplines; foster consistency in trial design, execution, and reporting; and improve outcomes through clarity and precision. Input and guidance was gathered from patients with kidney disease and their caregivers. Qualitative synthesis of thematic analysis from focus group interviews revealed the preference to discontinuation of 'end-stage' term as it causes fear of unknown, provokes undue trauma, implies impending death, and is obsolete. The term 'kidney failure' was less objectionable, although it still prompted concerns. Importantly, participants wanted more clarity about the severity of disease and prognosis, including quantitative descriptions of disease severity [14].

KIDNEY DYSFUNCTION REQUIRING DIALYSIS IS A HETEROGENEOUS ENTITY

Clinicians arrive at the diagnosis of KDRD using a range of signs, symptoms, and supportive laboratory tests. Comorbid illnesses play a large role both in the development of KDRD and in driving symptom burden [15,16]. Although many patients deemed to have KDRD have common patterns of clinical presentation – for example, impaired exercise tolerance or physical limitations in activities of daily living – their manifestations are widely heterogeneous; some patients can be relatively asymptomatic and have mild volume overload at GFR levels as low as 7 ml/min/1.73 m^2; other patients have significant volume overload at GFR 10–12 ml/min/1.73 m^2. As such, the diagnosis of KDRD is highly variable for similar levels of kidney function, leading to substantial variation in diagnosis thresholds across patients and physicians [17,18].

On account of KDRD heterogeneity, investigators have proposed its sub-categorization to catalyze more personalized dialytic therapies. For example, the sub-categorization approach proposed by Piccoli *et al.* considered a wide array of items (including, but not limited to, albumin, prealbumin, age, comorbidity index, residual kidney function, and interdialytic weight gain) [19▪]. As a step toward acknowledging disease heterogeneity, a simple shift to a more nuanced classification of the condition may support more tailored dialysis treatments and could be immediately beneficial to patients.

KIDNEY DYSFUNCTION REQUIRING DIALYSIS SUBCATEGORIZATION

KDRD categorization can have implications for treatment goals, in particular, for patients treated with in-center hemodialysis for whom thrice-a-week hemodialysis therapy is the norm. There is a need to recognize that many patients with incident KDRD still have residual kidney function yet all patients receive same level of hemodialysis therapy that does not align with their organism needs. Instead of the formulaic approach to prescribing expensive, burdensome hemodialysis treatments to all patients, therapy needs to be nuanced and adaptive to the needs of each individual.

From a pathophysiologic standpoint, patients with KDRD exhibit endothelial dysfunction, impaired metabolic homeostasis, immune system dysregulation, and chronic inflammation [20–23]. From a kidney function standpoint, a growing number of studies have shown that patients with ongoing residual kidney function can be treated with less-frequent schedules of dialysis [24–30]. Subtyping KDRD based on endogenous kidney function would support more physiological hemodialysis prescriptions congruent with a patient's current level of kidney function. Casino and Basile have identified thresholds of renal urea clearance (ml/min/351 or ml/min/1.73 m^2) for which the hemodialysis schedule can be prescribed as once-a-week; twice-weekly; or thrice-weekly [31,32▪▪,33]. Figure 2 displays a KDRD categorization model relying on similar kidney urea clearance thresholds, supplemented by thresholds of other biochemical parameters, urine volume, and symptoms, which could be used to support more personalized hemodialysis prescriptions.

For holistic phenotyping, other dimensions that indicate the degree of illness severity, such as patient-reported symptomatology and end-organ damage need to be incorporated. Patient symptomatology on dialysis and nondialysis days should be used to ascertain the adequacy of the dialytic therapy. The inclusion of other tubular secretory measures into current estimates of residual kidney function could help inform decision-making surrounding dialysis initiation and dialysis dosing in the setting of KDRD [34]. Surrogate markers of cardiovascular outcomes and death, such as left ventricular mass index and accurate blood pressure measurements as well as nocturnal blood pressure and dipping pattern obtained from 24-h ambulatory blood pressure, are also important considerations.

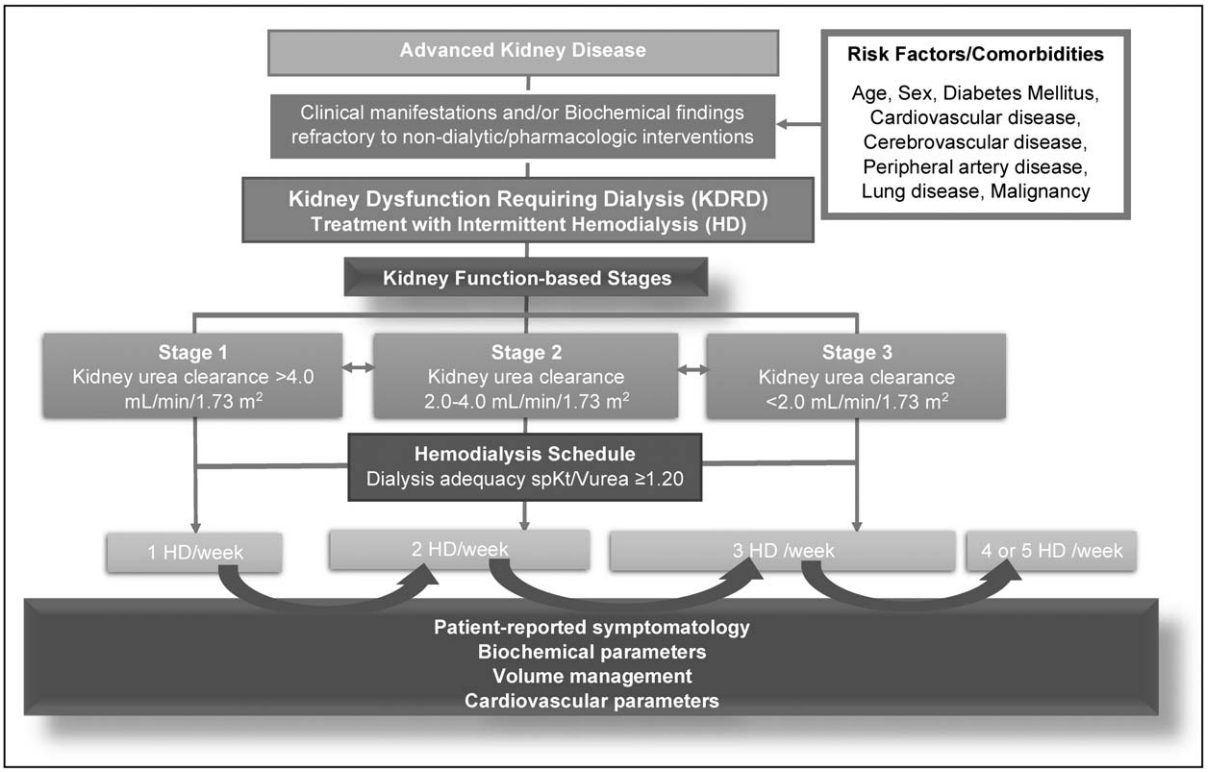

FIGURE 2. Progression of kidney dysfunction requiring dialysis based on levels of endogenous kidney function. Patients with advanced kidney insufficiency have a range of clinical signs and symptoms related to progressive volume overload and low solute clearance. Decision to diagnose kidney dysfunction requiring dialysis (KDRD) is commonly made on clinical and laboratory grounds of manifestations not manageable with dietary and pharmacological interventions. When in-center intermittent hemodialysis (HD) is elected as the treatment modality for KDRD, dialysis treatment could be guided by the severity of kidney failure estimated based on kidney urea clearance. Patients with less severe forms of KDRD – that is, stage 1 and stage 2 KDRD – could be treated with once-a-week or twice-a-week in-center HD. Akin to the clinical evolution of patients with chronic kidney disease, the patients in the spectrum of KDRD may advance in a sequential or leaping manner through ascending stages of severity; or progress to more severe stage and then revert to less severe stage with episodes of intercurrent illness; or remain in one or two stages of kidney dysfunction throughout their life. Risk factors/comorbidities play a role in the diagnosis, clinical manifestations, and the transition from early to advanced stages of KDRD. Patient-reported symptomatology, targeted biochemical parameters, volume management, and cardiovascular parameters are of paramount and overriding importance in adjusting HD prescription, independent of residual kidney function levels.

Left ventricular hypertrophy and hypertension are the most frequently observed cardiovascular abnormalities in patients with advanced kidney dysfunction and strongly predict cardiovascular mortality in patients on hemodialysis [35–37].

KIDNEY ASSISTANCE THERAPY BASED ON KIDNEY DYSFUNCTION REQUIRING DIALYSIS STAGES

Dialysis is a therapy that assists the kidneys in removing excess solutes and extracellular volume – rather than replacing their function. In spite of the technological and pharmacologic progress achieved in the field of dialysis, patients with KDRD on chronic dialytic therapy have a significant reduction in life expectancy compared with nondialysis-dependent counterparts [38,39]. Furthermore, conventional thrice-weekly hemodialysis has been embraced in clinical practice without being demonstrated that other hemodialysis schedules are inferior, particularly in patients with different states of illness severity and dialysis requirement [40]. Thus, the terminology kidney 'assistance' therapy rather than kidney 'replacement' therapy is more aligned with current deliverables.

Residual kidney function should not be the sole consideration in selecting the initial dialysis modality [41,42] as the quality of evidence comparing patient outcomes and the decline in residual kidney function across dialysis schedules is based on small, mostly single-center, observational studies [43]. In

addition to kidney urea clearance, other parameters ought to be used to tailor the hemodialysis prescription [40,44▪], such as achievement of target body weight (which is co-dependent on urine output), target clearance, cardiovascular function, and patient symptomatology [43,44▪,45]. Patients with persistent symptomatology related to volume overload on nondialysis days, uncontrolled hypertension or unachieved biochemical targets would be assessed for adjustments in dialysis schedule. With worsening cardiovascular parameters, such as rising left ventricular mass index or elevated ambulatory blood pressure in spite of adequate pharmacologic therapy, more frequent hemodialysis can be considered. The Frequent Hemodialysis Network Trial found that more frequent dialysis therapy (5 days per week) led to reduced left ventricular mass particularly in those with reduced residual kidney function [46,47]. Although these findings make a compelling argument for an incremental approach to dialysis frequency, it is important to note the degree of patient symptomatology and degree of change in cardiovascular parameters that should trigger changes in dialytic therapy will require definition in prospective studies.

SHOULD CLINICAL TRIALS CONTINUE TO ADDRESS ALL KIDNEY DYSFUNCTION REQUIRING DIALYSIS SIMILARLY?

Given the ambiguities in diagnosing KDRD, many challenges in adjudicating this diagnosis in clinical trials have been encountered [17]. To date, randomized trials of a variety of promising drugs and interventions have not been able to demonstrate clinical benefits in KDRD [46,48–56]. As KDRD has been considered a 'single-stage' homogeneous disease category, no distinctions have been made by level of endogenous kidney function among patients with KDRD included in clinical trials, potentially leading to differential intervention effects. Observational clinical studies have shown that higher levels of endogenous kidney function in patients with KDRD are associated with improved phosphate control [57], higher hemoglobin levels [58], better nutritional status [58,59], and better survival [60–63].

This raises the question as to whether clinical trials should be designed at including a better defined subcategory of KDRD for whom the intervention might be of most benefit. For a clinical trial to be successful, the right patients need to be matched to the therapies from which they are most likely to benefit. However, while targeting trials to specific phenotypes posited to respond to the tested intervention may increase the ability to identify efficacy, this approach may also limit ability to enroll enough patients for a sufficiently powered trial. Adaptive clinical trials hold the potential to increase the efficiency of randomized controlled trials in dialysis by identifying the patient population most likely to benefit from alternative hemodialysis treatment models, helping with sample size reestimation in potential scenarios when fewer patients may be required overall to ensure the same high chance of getting the right answer, or preventing an underpowered trial, which would mean a waste of resources [64,65].

In addition, as disease manifestation and symptom-based treatment approach is at the core of individualized dialysis treatment, patient engagement during study design and conduct is pivotal in order to build knowledge around their complex care management in health systems [66]. Furthermore, clinical trials with multistakeholder input (e.g. caregivers, providers, and administrators, in addition to patients) and mixed methods process evaluation can optimize implementation and sustainability of new hemodialysis therapy models [67,68]. Qualitative participant interviews can capture patients' experiences to better understand their views surrounding the dynamic nature of disease monitoring (e.g. serial timed urine collections for incremental hemodialysis prescription) and hemodialysis treatment delivery. Qualitative interviews with dialysis stakeholders can probe organizational and contextual factors that could affect real-world implementation and sustainability of individualized hemodialysis treatments.

FUTURE DIRECTIONS

It is important to acknowledge lack of robust data to support a stage-based approach to treatment of advanced stages of kidney failure with dialysis. A prerequisite for KDRD phenotyping is longitudinal data acquisition in large, well characterized cohorts [69]. This will enable characterization of distinct KDRD phenotypes, categorized by sociodemographic and clinical data, by using consensus clustering analysis [70]. Future clinical trials of KDRD should account for the heterogeneity of patients when considering inclusion/exclusion criteria and study design; and should *a priori* consider subgroup analyses to highlight specific KDRD subgroups that may derive greater benefit from a particular intervention. Furthermore, it will be interesting to identify degrees of KDRD clustering or endotypes in different KDRD stages and determinants of stage transition. Such studies can identify subpopulations of patients with KDRD that have different risks of KDRD stage progression, cardiovascular events and death. Of paramount importance in clinical trials is

to test whether tailoring hemodialysis prescription based on levels of residual kidney function and clinical symptoms is an effective and well tolerated approach. Of note, several ongoing clinical trials are using thresholds of kidney urea clearance, similar to those depicted in Fig. 2, to establish clinical effectiveness of less frequent hemodialysis in the form of once-weekly or twice-weekly hemodialysis vs. thrice-weekly hemodialysis [71–74,75▪▪].

Akin to methods of malignancy characterization, the phenotyping of KDRD should evolve with the study of associated biomarkers, improving the granularity of the phenotype. Identification of serum markers that reliably predict imminent KDRD progress from one stage to another will optimize dialysis treatment by eliminating the risk of underdialysis from delays in dialysis schedule intensification. Applying unbiased proteomics methods combined with disease-focused and hypothesis-driven approaches will be one way to push forward our understanding of KDRD phenotypes. Addition of metabolic readouts (metabolomics) will also be important, as these represent nutritional influences, important in patients with KDRD [76]. A system detailing specific, underlying biologic processes can assess the specific pathophysiological factors contributing to a patient's KDRD burden. For example, inclusion of molecular parameters of dysfunction in vascular beds, immune function, cytokines, and mitochondrial function may identify endotypes of patients within larger disease categories or stages. However, many of these variables are dynamic, so routine measurement followed by data synthesis may prove to be a formidable task.

CONCLUSION

Improved phenotypic characterization of KDRD, both in clinical practice and research settings, is critical if we are to improve outcomes and quality of life in this increasingly prevalent patient population. More nuanced terminology and our suggested staging model may support more patient-tailored and kidney failure stage-tailored dialysis prescriptions. Subtyping ought to be studied and refined in prospective studies to generate evidence-based approach to individualized dialytic therapy. Whatever scheme will be developed for KDRD phenotyping, it should be flexible (i.e. have the capacity to adapt to new findings) and practical (i.e. can be classified in a variety of settings), with the goal of driving specific therapies in distinct KDRD patients.

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Conflicts of interest

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In February of 2019, the Kidney Disease Improving Global Outcomes (KDIGO) committee held a Controversies Conference titled Blood Pressure and Volume Management in Dialysis to deliberate on blood pressure (BP) and volume management in individuals receiving maintenance dialysis. The overarching theme was that managing BP and volume in dialysis involves weighing multiple clinical factors and risk considerations as well as patient lifestyle and preferences. Balancing all these factors requires individualizing the dialysis prescription by incorporating comorbid health conditions, treatment hemodynamic patterns, clinical judgment, and patient preferences into decision-making, all within local resource constraints.

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