[Resource][Link to Dialysis]

Robertson, J, Senger, R et al., "Personalized Hemodialysis (PHD): An online treatment monitoring and adjustment system,"

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Executive Summary (Abstract): Personalized Hemodialysis (PHD)

Hemodialysis (HD) is a critical, life-sustaining procedure. However, new innovations are needed to achieve better patient health, higher quality of life/experience, reduced economic cost of care (i.e., more effective use of taxpayer and patient funds), and improved environmental impact. Personalized Hemodialysis (PHD) is a novel technology that addresses each of these points.

The idea behind PHD is that each patient's physiology is uniquely responsive to HD treatment, including: (i) variances in the rate of solute transfer between body compartments, (ii) rate of solute extraction in the dialysate, (iii) changes in body fluid composition and osmolality, and several others. Opportunities exist for HD treatments to account for these patient-to-patient differences. In current HD treatments, blood and dialysate are usually flowed at fixed flow rates through a dialyzer with a (generally) fixed dialysate composition and ultrafiltration rate. This leads to rapid urea and small molecule removal at the beginning of an HD treatment, and this clearance rate decreases over the course of treatment. PHD technology represents a new approach to HD treatment where spent dialysate (i.e., waste dialysate) molecular composition and osmolality are monitored continuously in real-time to respond to the individual patient's dialysis process, and these data are combined with patient biofeedback (i.e., health and well-being during the HD treatment). These then inform an automated process controller that adjusts the dialysate flow rate of HD treatments to optimize removal of solutes across all sizes and protein binding states while minimizing osmotic shifts and conserving use of dialysate. With PHD we are able to (i) specifically control and maintain the rate at which patients' clear urea and other small molecules over an entire treatment and (ii) conserve up to 50% of the dialysate needed for a single HD treatment.

Our team of engineers, physicians, and research scientists has already made significant strides in developing a PHD technology prototype. The system is designed to work with any current HD machine and does not interfere with current standard HD treatment or patient care.

Patients in crisis: The pressing need for HD innovations

Over 530,000 Americans depend on HD; patients with end-stage renal disease (ESRD) suffer and die without it[1]. HD is costly in humanitarian and economic terms (>$34B annually, subsidized extensively by taxpayers). The vast majority of HD patients report significantly diminished quality of life, revolving around the treatment cycle (preparing for treatment, treatment, recovering from treatment), according to care providers and patient advocates (personal communication, AAKP.org). Complications and side effects associated with HD treatment are common, including: (i) profound, immediate, and then persistent fatigue; (ii) gastrointestinal disturbances; (iii) altered mentation/memory loss; (iv) muscle cramping; (v) itching; (vi) anemia; and (vii) volume and electrolyte imbalances. The underlying causes of many of these complications and treatment-related side effects are not well-understood, making management difficult.

Even with HD treatments, the lives of ESRD patients are shortened dramatically, and their five-year survival rate is less than 40%[1]. Some patients (e.g., those with poorly controlled diabetes) only survive 1-2 years after starting HD. Other patients live 10-20 (or more) years on

HD therapy; although, caregivers have not been able to identify common factors correlated with long-term survival. Put simply, standard "One-size-fits-all" HD therapy is a critical but imperfect therapy that is associated with high morbidity and mortality, and poor quality of life for patients[2].

The concept of "One-size-fits-all" HD therapy is logically flawed

HD therapy typically consists of a standing prescription (e.g., 3x weekly, 3-5 hours per treatment), which may be changed on a monthly basis (at the maximum) but rarely changes from treatment to treatment. The overarching goal of the HD prescription is achieving urea kinetic targets (Kt/V), coupled with adequate fluid removal. Occasionally, providers make adjustments to improve phosphorus clearance (increased time) or fluid removal tolerability (sodium modeling), but these changes are then implemented for subsequent treatments, rather than changing from treatment to treatment, based on individual treatment needs of the patient.

The "One-size-fits-all" HD prescription has resulted in several stumbling blocks in innovation.

First, the "urea-centric" approach to HD has made it difficult to see beyond urea as "the" marker of efficacy or to appreciate the significance of the clearance of other solutes in patient health. The HEMO study[3] suggested that achieving higher urea clearance kinetics did not alter mortality for most groups, suggesting a role of other molecules (e.g., "uremic toxins" such as indoxyl-sulfate) and/or proteins (e.g., β2-microglobulin). Numerous studies suggest these other molecules have an important role in the deterioration of renal failure patients.

Second, there are multiple problems with using urea kinetics as the sole determinant for most components of the HD prescription, including the observation that urea reduction ratio (URR) and Kt/V can vary considerably from treatment to treatment[2]. Lacking the ability to quantify mass transfer of solutes on a large scale has inhibited the ability to study the effects of their removal on patient outcomes. For example, what if a single treatment for phosphorus removal revealed a linear correlation with cardiovascular mortality? This might influence subsequent treatment prescriptions. PHD technology enables real-time measurement of solute clearance of molecules of varying weight and size, allowing us to study the relationship between solute removal and clinical outcomes on a large scale. This information will then be used to optimize patient outcomes.

Third, fixed HD treatment parameters may produce unnecessary solute shifts, causing patient discomfort in the form of cramping and HD intolerance. We have gathered real-time molecular composition data of waste dialysate generated during HD treatment of six patients (three males, three females). This was done using Raman spectroscopy and our proprietary Rametrix® technology[4-6] (a key component of PHD technology, discussed later). When using it to monitor HD treatments, we observed quantities of small molecules (i.e., urea, creatinine, amino acids) in the spent dialysate near the beginning of treatment (15 minutes), middle (90 min), and near end (180 min). A Raman scan of spent dialysate is shown in **Figure. 1A**, and results for urea are shown in **Figure. 1B**. **Finding:** HD removed urea from all patients at different rates, and the most substantial urea extraction was at the beginning of treatment. **Interpretation:** Rate of urea extraction (i.e., flux) is not linear throughout an HD treatment and changes from patient-to-patient. The urea extraction flux is very high during the beginning of HD treatment and becomes very low towards the end of the treatment. **Potential application:** Use of lower blood and dialysate flows at the beginning of treatment and rise gradually over time will distribute urea removal flux throughout an entire HD treatment and may better prevent osmolar shifts that result in patient cramping and dialysis intolerance. Constant online monitoring of osmolality and spent dialysate with Rametrix® and adjustment of the dialysate flow rate (or other parameters) with PHD will optimize this process.

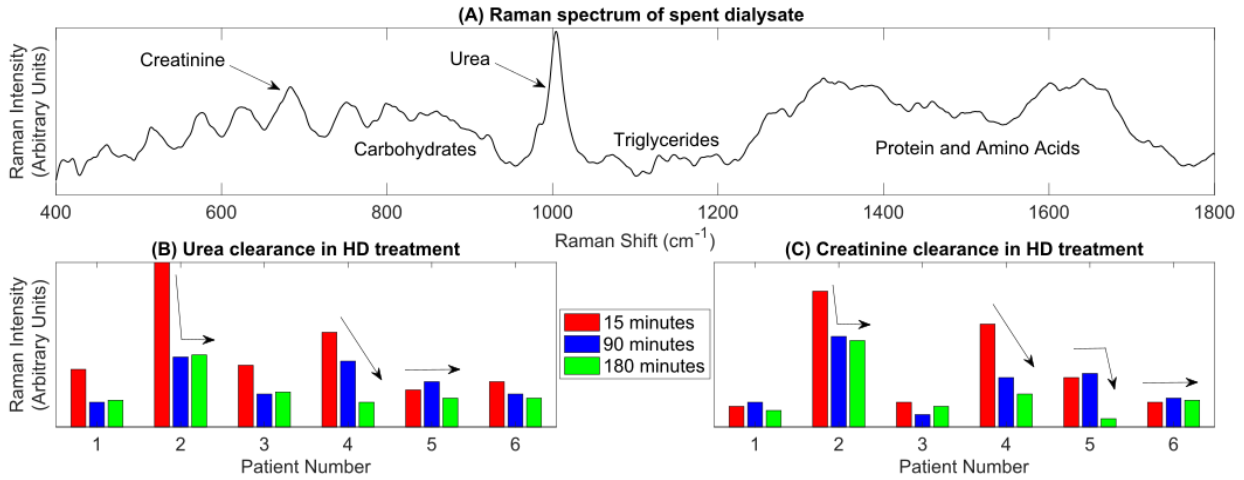

Figure 1. (A) Rametrix® processed Raman spectrum of spent dialysate with broad identification of bands, (B) Rametrix® measured urea concentrations in spent dialysate during HD treatments (at 15, 90, and 180 minutes) for 6 separate patients, and (C) measured creatinine levels in spent dialysate. Raman intensity (arbitrary units) is shown on the y-axis of all plots. This is directly related to concentration.

Furthermore, by studying changes in osmolality in spent dialysate, we hope to identify risk factors for cramping and dialysis intolerance, which have been identified as some of the most troubling symptoms for HD patients. A sharp decrease in osmolality could be treated with a brief infusion of hypertonic saline or a transient increase in dialysate sodium in order to prevent the symptom. If the patient were to feel the symptoms of a cramp or headache starting, they could also activate a biofeedback-based mechanism to inform PHD to make similar interventions or further slow the rate of small molecule clearance.

We also extracted creatinine clearance data from the Rametrix® measurements for the patients described above. Results are shown in **Figure. 1C**. **Finding:** The pattern of creatinine extraction did not mirror urea extraction, despite the fact that both urea and creatinine are small, readily-dialyzable molecules. **Interpretation:** The kinetics of creatinine extraction vary by patient and gender. **Potential application:** For removal of molecules of this size, dialysate flow could potentially be reduced early in the treatment when the diffusive gradient is high, thus saving dialysate, improving the economics of HD treatments, and reducing environmental impact.

We found similar disparities in the rate and timing of molecular extraction when we examined Rametrix® data for other small molecules, such as amino acids.

Fourth, dialysate flow rates are often set at 1.5x the blood flow rate to maximize the urea clearance. However, if dialysate flow rates varied throughout HD treatment based on targeting solute clearance measurements in the spent dialysate, potentially large amounts of dialysate could be spared, leading to significant cost savings for HD treatments (discussed below).

PHD technology: Concept …driving prototyping and testing

We believe every patient needs personalized HD (i.e., PHD) treatment every time they are dialyzed. We have designed, prototyped, and tested PHD technology for monitoring and adjusting HD treatment in real-time. There are three interactive components in PHD technology:

- We use high-throughput Raman spectroscopy (Rametrix®) for real-time (i.e., during HD treatment) analysis of the molecular composition of spent dialysate (post dialyzer). Rametrix® allows us to analyze the “efficacy” (i.e., quantity, type, and timing) of waste

molecule extraction during an HD treatment. We have validated Rametrix® extensively [**Links to Resources**].

- We designed, built, and tested a sensor retrofitted to the spent dialysate line of HD machines. This sensor module intermittently collects samples of flowing spent dialysate so the molecular composition can be determined by Rametrix® during HD treatment.
- We designed, built, and tested a device to control the flow of dialysate during HD treatment.

Preliminary data in the laboratory (non-clinical) with a synthetic blood mixture (i.e., water, urea, creatinine, and glucose) has shown that our devices and approach reduce the amount of dialysate used during each HD treatment (currently 120-140 liters of ultrapure dialysate per session) by up to 50%, while clearing the same amount of urea. If implemented in a clinical setting, this would reduce the cost and water consumption of every HD treatment. Dialysate conservation may be especially critical in sustaining HD treatments during natural disasters. Hurricanes Katrina, Maria, Irma, and Michael severely impacted the availability of fresh water for on-site formulation of dialysate. Reduced dialysate requirements might allow pre-mixed dialysate to be transported to available or local, temporary patient care sites, rather than having to move patient hundreds of miles to already overburdened facilities.

PHD technology: Innovation

Our PHD innovation provides novel approaches to problems facing patients and frustrating their caregivers.

- ***The technology strives to replicate some kidney functions***
    - **Fluid regulation; filtrate drainage and connectivity** – PHD can monitor the molecular composition of spent dialysate. This allows adjustment of the flow rate of dialysate and the rate of removal of excess body water from patients incrementally.
    - **Toxin removal and secretion** – Currently, it is unknown what uremic toxins are present in each individual patient, how much of the uremic toxin burden is dialyzable, and/or if reduction in dialyzable toxins is correlated with patient outcomes and quality of life. The Rametrix® Module allows detection of some dialyzable toxins (i.e., we have obtained Raman spectra for some, including indoxyl-sulfate). Note, Raman scans provide information on the spent dialysate "metabolome" (i.e., all molecules present). We expect to relate the presence of individual Raman bands to patient outcomes. This is a strategy to discover "biomarkers" (consisting of one or multiple molecules) of long-term patient outcomes.

- ***The technology has been developed to improve patient quality of life***
    - **Minimizing burden on family and care partners** – We believe strongly that if we can personalize appropriate length and frequency of HD treatments (not "One-size-fits-all") for every patient, we may succeed in **reducing both the burden of treatments and the treatment cycle** (i.e., fewer treatments, appropriate duration of treatments, interval of treatments).
    - **Improving ability to work, travel, engage in recreational activities** - By reducing both the burden of treatments and the treatment cycle, this is going to help **align treatment to patient needs and lifestyle aspirations**. We also anticipate PHD will bring about improved patient health and well-being.

- **Reducing disease and treatment complications** – It is currently extremely difficult to determine the progressive effects of ESRD and important co-morbidities (e.g., diabetes and hypertension) on individual patients. These diseases and co-morbidities have a major impact on HD treatments including: how much is needed, when it is needed, or if it is working. "One-size-fits-all" leaves many ESRD patients under-treated, over-treated, or effectively untreated. PHD technology allows every treatment to be tailored to individual patient needs and health status. One important goal of personalized treatment is **keeping patients as healthy as possible** while awaiting transplantation while also providing the **best quality of life** possible. We recognize that treatments need to evolve with progressive disease and PHD provides objective, functional, real-time data for patient management and decision-making. As noted, a relatively poor understanding still exists between the relationship of the individual patient and treatment-associated complications. PHD will allow correlation of treatment metrics with incidence and severity of complications, and whether treatment modifications can improve the condition.
- **Providing more choices for treatment** – PHD can be readily adapted for in-center or home HD treatments. In fact, PHD may provide an ideal means to monitor (via wireless communication) individual home HD treatments and provide a means to alert/intervene (in real-time) if problems are encountered during a treatment. Cutting dependence on in-center HD treatment and the freedom attendant with home HD use could be beneficial for many ESRD patients. A shared goal of regulators, providers, and caregivers **is to increase the use of home HD services**. Integration of PHD monitoring could increase patient confidence and decrease anxiety with home HD, foster patient compliance and management, and extend the "reach" of nephrologists and caregivers through integrated PHD telemedicine technologies.
- **Liberalizing diet and fluid regulation** – PHD provides both patients and caregivers objective metrics on how lifestyle choices affect the "starting point" of each HD treatment. It seems likely that although historical experiences and research have guided current diet and fluid intake guidelines, like the HD prescription, these "One-size-fits-all" guidelines may not have the same (beneficial) effects for every patient. It is quite possible that caloric and protein restrictions that stabilize one patient may not stabilize others. This would result in a discernible, abnormal molecular profile when HD treatment is started, which would likely require dialysate flow rate adjustments by PHD to meet patient molecular clearance targets.
- **Reducing medication burden** – PHD can detect the presence of dialyzable medications (e.g., vancomycin, opioids, etc.) and nutrients (e.g., amino acids). Using Rametrix® data, we can more accurately predict how much medication is retained between treatments, how much is lost during dialysis, and how much needs to be supplemented following treatment. This will help optimize the use of medications and reduce wasteful dosing, thus improving HD cost-efficiency.

- ***The technology employs novel biosensors and other safety monitoring functions***
  - **Sensing** – As described, a Raman-based real-time sensor is a key component of our system. We have designed, prototyped, and tested this sensor and Rametrix®.
  - **HD machine safety checks** – PHD and Rametrix® can be used (during operation and in real-time) to assess the integrity of HD machines, readiness for HD therapy, and detect the presence of contaminants (e.g., hemoglobin or trace solvents in consumables) that can trigger complications during treatment.

- **Dialyzer safety checks** – Some facilities re-process and reuse dialyzers. The cleanliness of these reused dialyzers and the potential presence of residual solvents and cleansing agents are currently difficult to evaluate. We can assess the quality and thoroughness of preparation of these re-processed dialyzers prior to their use with Rametrix®. This will help assure patient safety.

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