Received: 19 September 2022 | Revised: 29 November 2022 | Accepted: 12 December 2022

DOI: 10.1002/ntls.20220048

Natural Sciences

RESEARCH ARTICLE

# Identification of end-stage renal disease metabolic signatures from human perspiration

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**Funding information**
Precision Health & Integrated Diagnostics Center; Multidisciplinary University Research Initiative (MURI) program, Grant/Award Number: AFOSR FA9550-21-1-0170; National Institutes of Health, Grant/Award Numbers: U54DK10255603, 5RM1HG00773508

## Abstract

End-stage renal disease (ESRD), characterized by cessation in kidney function, has been linked to severe metabolic disturbances, caused by the buildup of toxic solutes in blood. To remove these solutes, ESRD patients undergo dialysis. As a proof of concept, we tested whether ESRD-related metabolic signatures can be detected in perspiration samples using a combined methodology. Our rapid methodology involves swabbing a glass slide across the patient's forehead, detecting the metabolites in the imprint using desorption electrospray ionization mass spectrometry, and identifying the key differences using machine learning methods. Based on collecting 42 healthy and 27 ESRD samples, we find saturated fatty acids are consistently suppressed in ESRD patients, with little change after dialysis. Moreover, our method enables the detection of uremic solutes, where we find elevated levels of uric acid (6.7 fold higher on average) that sharply decrease after dialysis. Beyond the study of individual metabolites, we find that a lasso model, which selects for 8 $m/z$ fragments from 24,602 detected analytes, achieves area under the curve performance of 0.85 and 0.87 on training ($n = 52$) and validation sets ($n = 17$), respectively. Together, these results suggest that this methodology is promising for detecting signatures relevant for precision health.

KEYWORDS
end-stage renal diseaseymachine learning, lipids, mass spectrometry, perspiration

## Key points

- Combines physical measurements with statistical analysis based on machine learning.
- Uses results to make medical predictions.
- Learns about biological pathways.

## INTRODUCTION

Sweat-based diagnostics promise to improve precision health,[1] where individual health outcomes can be improved through the noninvasive monitoring of specific physiologically relevant chemical signatures[2–4] that can predict disease risk and onset. Previously, sweat-based diagnostics have only been clinically employed for the measurement of sweat chloride levels in cystic fibrosis,[5] due to challenges in reliably measuring a broad array of analytes and understanding which specific ones robustly predict disease.

Realization of sweat-based diagnostics will require understanding the relation between sweat analyte levels and health status.[3] Recent examples have highlighted several possibilities in linking sweat analytes with health status, including tracking sweat uric acid levels for gout,[6] cortisol and cytokine IL-6 levels for stress,[7] and lactate levels for physical fatigue and tissue oxygenation status.[8] These approaches share limitations that motivate our work. Notably, these examples along with current sweat chloride clinical measurements in cystic fibrosis are restricted to tracking a couple of specific analytes and require knowing beforehand which analytes are related to disease. In contrast, as a proof of concept, this work applies a simple and rapid unbiased methodology to collect human perspiration samples based on swabbing a glass slide across an individual's forehead, mass spectrometry methods for detecting a broad set of metabolites in samples, and machine learning approaches for identifying the key metabolic signatures related to end-stage renal disease (ESRD).

ESRD, the final stage of chronic kidney disease, is characterized by cessation of kidney function and profound metabolic disturbances,[9] particularly metabolic acidosis, serum lipid abnormalities, changes to glucose homeostasis, and proteinuria. Globally, chronic kidney disease has an estimated prevalence of 13.4% and results in 2.6 million deaths, where over 10% of individuals will progress to ESRD.[10,11] Within the United States, chronic kidney disease is estimated to affect over 37 million Americans, where diabetes and blood pressure are often risk factors for ESRD progression.[12] Because of the high disease burden and possibility of misdiagnosis through a routine clinical assessment of chronic kidney disease status using the proteinuria and estimated glomerular filtration rate (eGFR),[8,13] identifying robust metabolite changes, which are known to be associated with chronic kidney disease progression, has great potential for improving diagnosis and managing kidney disease by providing novel biomarkers.

Ideally, sweat-based diagnostics in this context can guide the clinical management of chronic kidney disease progression. However, as little is known about changes in the sweat profile from kidney dysfunction, this work assesses the feasibility of noninvasively detecting aberrant metabolic signatures in sweat that are associated with ESRD.

Using our combined methodology, we are able to detect and identify 13 saturated fatty acids, of which 2 exhibit statistically significant suppression in ESRD patients compared to healthy controls. Our analysis also enables the detection of uric acid, a known uremic solute, that is elevated in ESRD patients' sweat profiles before dialysis and at significantly lower concentrations after dialysis. Beyond the study of specific metabolites, a binary logistic regression lasso classifier selects 8 analytes from 24,602 that achieve 88.4% accuracy using cross-validation (52 samples) and 82.4% accuracy on a holdout test set (17 samples). Although most studies in sweat focus on specific known metabolites, these findings are unique to our analysis, which enables a unbiased selection of important metabolic signatures for possible diagnostic use without defining the metabolites beforehand. Together, these findings suggest our sweat methodology can specifically detect metabolic changes that are characteristics of ESRD and more generally enable precision health noninvasive monitoring and disease diagnosis.

## RESULTS

### Identification of ESRD-associated metabolic signatures in sweat using DESI-MS

To identify ESRD-associated metabolic signatures in sweat, we used a four-step approach (Figure 1). Forty-two healthy donor samples were collected, including 20 healthy control individuals from the Integrated personal omics study.[14,15] Additional 27 samples were collected from 13 individual ESRD patients from the Palo Alto Veterans Affairs Hospital. Sample collection details and the clinical characteristics of both patient groups are summarized in Supporting Information and Table S1, respectively. The study was approved by Stanford University's Institutional Review Board and follows the tenants of the Declaration of Helsinki. Next, in contrast to sweat chloride measurements that involve active chemical stimulation of sweat, our collection procedure involved simply pressing and swabbing an ethanol-cleaned and dried glass slide on each patient's forehead. This method, which is highly noninvasive and takes ~5 s to perform, can directly capture the chemical products of human sweat on the skin surface.[5,16] For ESRD patients, sweat samples were collected immediately before hemodialysis. After sample collection, desorption electrospray ionization mass-spectrometry (DESI-MS) was applied to the slides with no additional sample preparation, which enabled the detection of 24,602 analytes in the mass spectrometer. An internal standard, sodium taurocholate ($m/z$ 514.28), was incorporated into the electrospray solvent to help account for technical variability between spectra. Further, mass spectra corresponding to sweat samples were compared with those from blank slides to ensure sweat analytes were derived from samples (Figure S1). Statistical analysis was subsequently conducted to identify the important differences between groups. After the normalization of peak abundances with respect to the internal standard, an application of significant analysis of microarrays (SAM; 15) and statistical LASSO methods were applied on processed[17] spectra to identify differences between healthy controls and ESRD patients. For model training and evaluation, samples were split into training ($n = 52$) and test ($n = 17$) splits, where the training set was used for initial metabolite analysis and comparisons. We identified a total of 167 different peaks between ESRD patients and controls using SAM, of which over 94% of the peaks are upregulated in ESRD samples (Figure 2a).

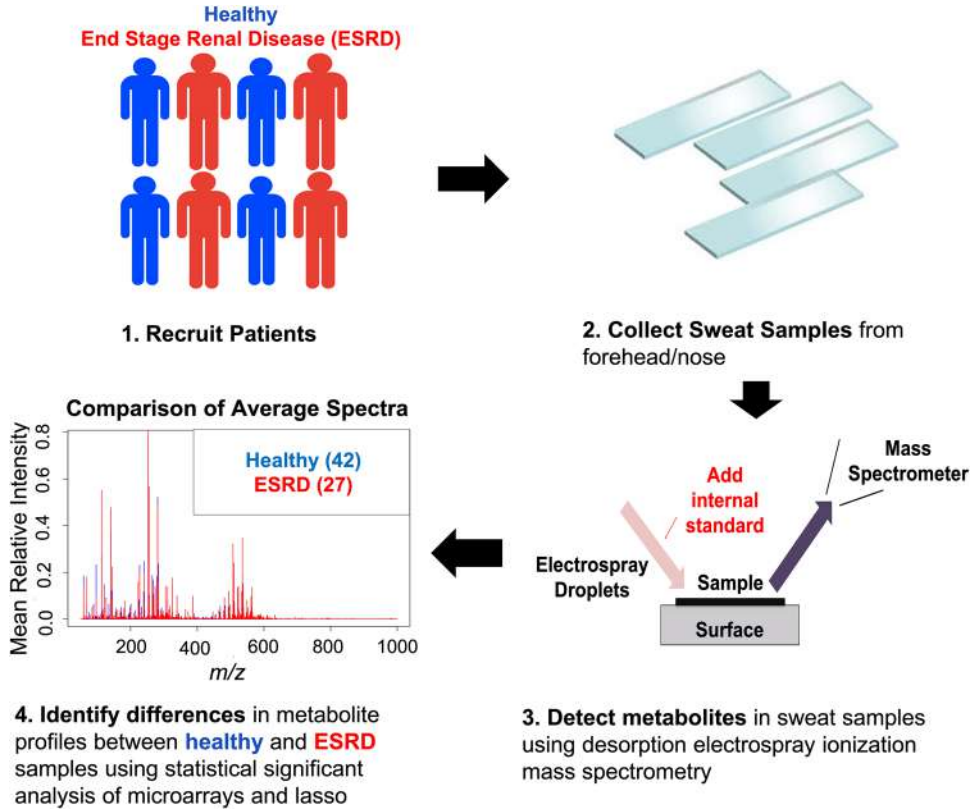


**FIGURE 1** Overview of the four-step methodology, where (1) healthy controls ($n = 42$) and end-stage renal disease (ESRD) patients ($n = 13$) are recruited, (2) sweat samples are collected from each donor by swabbing a cleaned glass slide across the forehead/nose, (3) desorption electrospray ionization mass-spectrometry (DESI-MS) is used to detect and quantitate metabolites in sweat samples, and (4) statistical methods are used to identify differences between the healthy (42) and ESRD (27) sweat samples.

As our methodology uses low sample volumes for detecting sweat analytes, sweat metabolites were identified using a combination of strategies. First, we conducted collision-induced dissociation tandem mass spectrometry experiments to obtain the fragmentation profile of specific peaks. To identify the metabolites, the parent peak, along with the fragmentation spectra, was compared with multiple databases, including LIPIDMAPS (https://www.lipidmaps.org), METLIN (https://metlin.scripps.edu/), and Human Metabolome Database (https://hmdb.ca/). Additionally, based on pooled sweat samples from six healthy donors, hydrophilic interaction mass spectrometry (HILIC-MS) experiments were conducted, where peaks were identified based on matching retention times and *m/z* values with a mixture of analytical grade standards.[18] Additional methodological details are provided in Section SI and information used to identify metabolites is listed in Table S2.

## Saturated fatty acid levels are consistently suppressed in ESRD donors' sweat

Saturated fatty acids have been consistently identified as some of the most abundant metabolites in sweat,[5,16,19] and impaired fatty acid $\beta$-oxidation metabolism has been implicated with advancing chronic kidney disease.[20] Based on these observations, we examined whether levels of saturated fatty acids in sweat profiles differ between healthy controls and ESRD patients. Each saturated fatty acid was identified using tandem mass spectrometry and comparisons to analytical standards (Figures S2–S14). The median levels of 13 saturated fatty acids (C6:0–C18:0) were consistently reduced in ESRD donors' sweat compared to those from healthy controls (Figure S18). Specifically, compared to ESRD donors, healthy controls have saturated fatty acid levels ranging from 3% higher (margaric acid C17:0 *m/z* 269.24) to 84% higher (lauric acid C12:0 *m/z* 199.16) on average (Figure S18). To address the multiple comparisons problem when comparing 24,602 analytes, SAM,[21] which estimates the false discovery rate using permutation tests, was used to compare healthy and ESRD sweat profiles, and SAM identified lauric acid (*m/z* 199.16) and stearic acid (*m/z* 283.26) as statistically significant differences between groups (false discovery rate <5%) (Figure 2b).

To determine if hemodialysis resolves these lipid differences, we compared sweat samples collected from two donors immediately before and after dialysis (Figures S15 and S16). Interestingly, our analysis reveals that most saturated fatty acids, in comparison to all detected analytes, do not significantly change after dialysis (Figure S16). Although the average percent difference among detected analytes between post- and pre-dialysis samples in relative intensity is 122.6%, lauric acid (C12:0 *m/z* 199.16) and stearic acid (C18:0 *m/z* 283.26) have an average percent difference of 26.8% (24.9% percentile) and 16.5% (15.5% percentile), respectively.

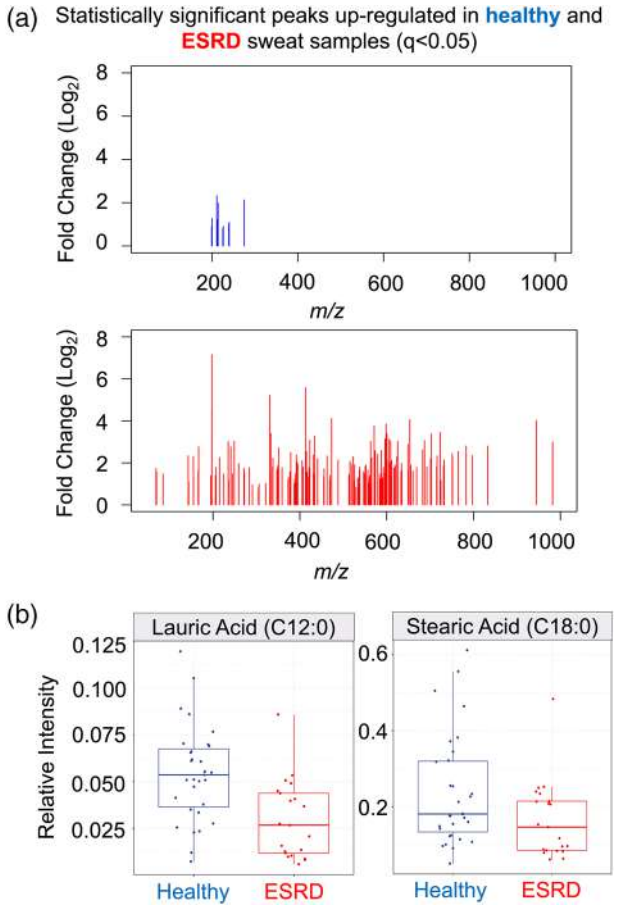


**FIGURE 2** (a) Significant analysis of microarrays (SAM) was employed to identify statistically significant differences in metabolite abundances between healthy and end-stage renal disease (ESRD) donors. Over >94% of SAM-selected peaks are upregulated in ESRD samples (red), whereas the remaining are upregulated in normal (blue). (b) SAM identifies statistically significant differences in the concentrations of lauric acid C12:0 (*m/z* 199.16) and stearic acid C18:0 (*m/z* 283.26), where levels are 84% and 44% higher on average in healthy controls compared to ESRD donors, respectively.

To identify additional fatty acid peaks in sweat samples, HILIC-MS was conducted on six pooled sweat samples from healthy donors (Supporting Information). Based on matching retention times and detected *m/z* fragments with analytical standards, we also detect hydroxy saturated fatty acid levels for C6:0, C8:0, and C12:0 are slightly elevated in healthy donors compared to ESRD patients (Figure S19), with median fold change ranging from 1.71 for C6:0 to 3.14 for C8:0.

From HILIC-MS data, we also detected the minor suppression of small-chain fatty acids in ESRD donors, specifically butyric acid (*m/z* 87.0) (Figure S19). Although we did not find any statistically significant differences in butyric acid levels between healthy donors and ESRD patients, our findings carry additional implications. Butyrate is one of the most abundantly produced gut bacteria–derived metabolites (estimated luminal concentration 10–20 mM) that mediates inflammation and colonic homeostasis.[22] Based on this data, we surmise that changes to small chain fatty acids related to the gut microbiome may also be detected using our methodology.

From these results and the finding that SAM does not detect significant differences in saturated fatty acid metabolite levels between pre- and post-dialysis samples, we infer that saturated fatty acid dysregulation is a robust phenotype of ESRD, which can be detected via sweat and does not change based on dialysis. Additionally, because neither lauric acid nor stearic acid levels among ESRD donors are associated with the length of time on dialysis (Figure S20), it suggests these metabolic changes are characteristic of all ESRD patients in this cohort. Moreover, our findings agree with independent clinical studies on dyslipidemia, which has been established as a known hallmark of chronic kidney disease that worsens during disease progression.[23,192]

## Uric acid, a known uremic solute, is elevated in sweat profiles of ESRD patients

Multiple metabolomics studies[24,25] have found that uremic solutes accumulate in the plasma of ESRD patients, which are associated with kidney dysfunction. Therefore, we next evaluated if any of these solutes could be detected in sweat. Of the hundreds of known uremic solutes,[24] uric acid is of particular interest because it has been identified as a direct contributor to kidney injury[26] and implicated as an independent predictor for ESRD.[26,27]

As shown in Figure 3, uric acid (*m/z* 167.0) is detected in both the sweat profiles of healthy and ESRD patients. Tandem mass spectrometry experiments and a comparison of retention time and *m/z* with known analytical standards were used to assign the uric acid peak (Figure S17). Comparing patient groups, SAM identifies that uric acid levels are significantly higher in ESRD patients (6.7 fold) compared to healthy controls ($q < 0.05$) (Figure 3a). As hemodialysis has been found to achieve >60% efficacy in serum uric acid clearance,[28] we assessed how uric acid levels change in sweat profiles of two ESRD patients immediately after dialysis. Consistent with serum studies, we find in one patient no uric acid levels after dialysis (SV5B) (100% decrease) and a 56% reduction in uric acid levels in another patient (SV9B). These differences highlight that significant changes in serum metabolites are reflected in the sweat profile and can be captured using our methodology (Figure 3b). Similar to lauric and stearic acid comparisons, we find that uric acid levels do not significantly change based on the length of time on dialysis (dialysis vintage) (Figure S20), suggesting the elevated uric acid levels in predialysis samples is a shared hallmark for most ESRD patients in this cohort.

Additionally, as serum uric acid levels are associated with creatinine and urea nitrogen levels,[29] which are widely used clinical markers of kidney function, we compared uric acid in sweat with blood urea nitrogen and creatinine levels (Figure 3c,d). As shown in Figure 3c,d, there are significant associations between sweat uric acid levels and blood urea nitrogen ($R = 0.69$, $p = 3.9e-06$) and creatinine ($R = 0.75$, $p = 2.4e-07$) levels. Although sweat uric acid, blood urea nitrogen, and creatinine levels are markedly different between healthy and

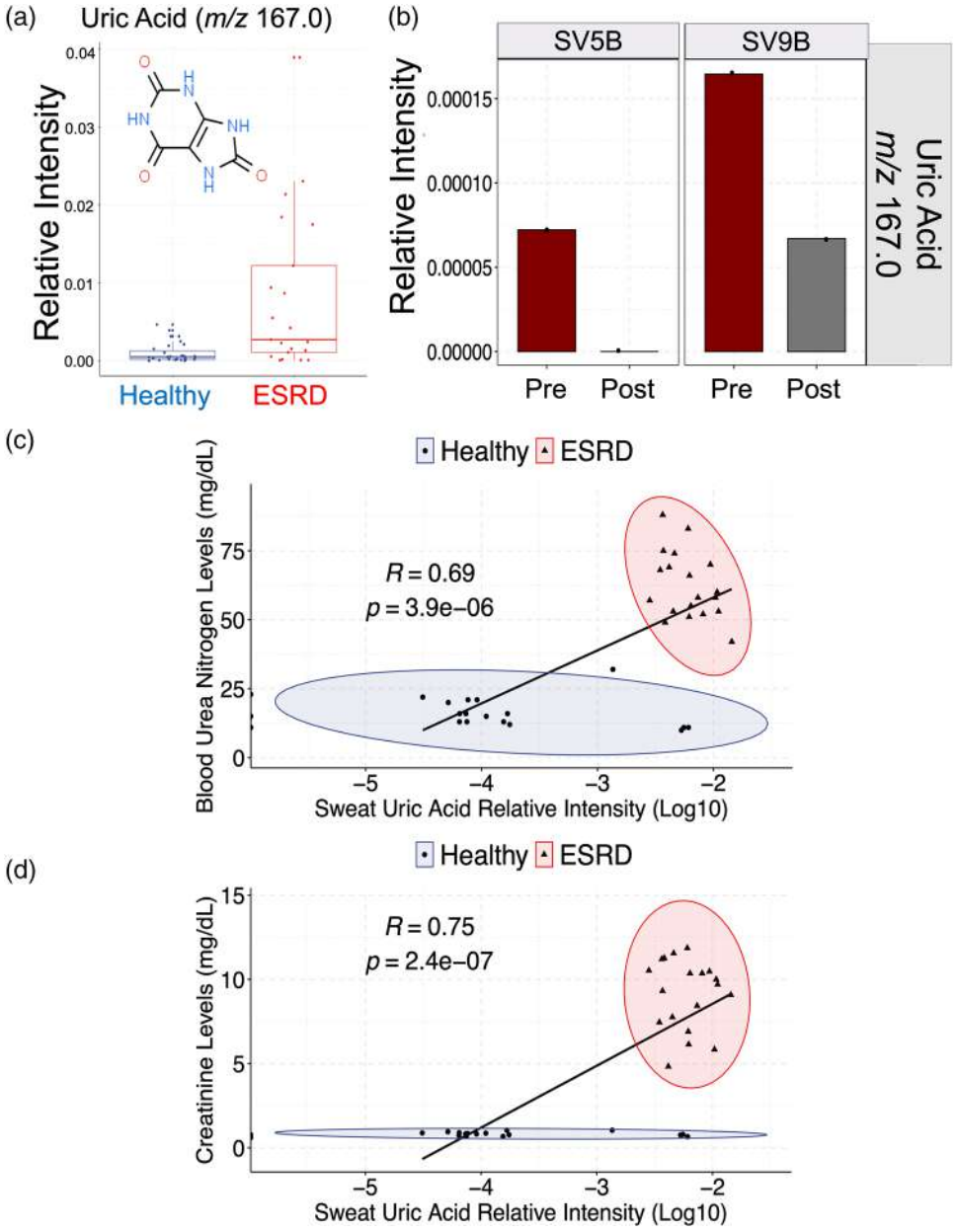


**FIGURE 3** Study of uric acid levels in sweat: (a) sweat uric acid (*m/z* 167.0) levels in healthy and end-stage renal disease (ESRD) subjects; (b) comparison of uric acid levels in sweat from samples collected immediately before and after hemodialysis for two donors (identified as SV5B and SV9B); (c) correlation of clinical blood urea nitrogen levels (mg/dl) and sweat uric acid relative intensity levels (log10 transformed); and (d) correlation of creatinine levels (mg/dl) and sweat uric acid relative intensity levels (log10 transformed). Each dot in (a), (c), and (d) corresponds to a unique patient

ESRD patients, sweat uric acid levels exhibit notable heterogeneity, especially among samples from healthy donors (Figure 3c,d). In contrast, all ESRD patients cluster together by sweat uric acid, blood urea nitrogen, and creatinine levels, where blood markers have greater variability than sweat uric acid levels within this group. Further analyses of healthy donors with highest uric acid levels (the three rightmost patients on the blue ellipse, Figure 3c,d) based on blood glucose (HbA1c) or cholesterol levels (HDL, LDL) did not identify any distinguishing features. Although it appears that uric acid levels in sweat do not match the heterogeneity of blood markers *within* each patient group (i.e., healthy, ESRD), these results support that differences in kidney function between groups can be captured through the chemical analysis of sweat.

## Machine learning with the lasso identifies metabolic signatures that stratify healthy and ESRD patients

With 24,602 total detected features, studying the differences in specific individual metabolites between groups is highly limited.

Therefore, to assess if sweat-derived metabolic signatures can distinguish healthy from ESRD patients, we trained a binary logistic regression lasso classifier. Importantly, as the lasso returns a sparse model, it can select for the key metabolic signatures without knowing beforehand the important set of biomarkers that stratify healthy and ESRD patients. Additionally, the lasso is readily interpretable because the selected model coefficients can help inform which peaks are most important for the classification. To train the model, samples were split into training and test sets, with 52 and 17 sweat samples, respectively. The model performance was evaluated within the training set using leave one patient out cross-validation and separately assessed on the independent test set. Additional details are provided in the Supporting Information section description.

The lasso binary logistic classifier selected 8 *m/z* fragments (Figure S21) that achieve 88.4% overall cross-validation accuracy and 82.4% accuracy on the holdout validation set (Table S3). Table S3 also shows that the model achieves 80.9% and 66.7% sensitivity and 90.3% and 90.9% specificity on training and validation sets. Sensitivity corresponds to the true positive rate [(true positives)/(true positives + false negatives)], and specificity corresponds to the true negative rate [(true negatives)/(true negatives + false positives)]. To obtain a more informative view of the model sensitivity and specificity, receiver operating characteristic area under the curve (ROC-AUC) analysis was conducted (Figure 4a). Although sensitivity and specificity reflect the model's performance at a particular threshold, the AUC (i.e., ROC curve) metric across multiple thresholds provides a more comprehensive view of the model's diagnostic performance. As shown in Figure 4, the lasso model achieves ROC 0.85 ± 0.06 on the training set and 0.87 ± 0.11 on the validation set. In addition to the stable model accuracy across training and validation sets, the comparable AUC values affirm that the model performance appears stable across a separate group of patients. More broadly, our results underscore that metabolic signatures derived from human perspiration samples can distinguish healthy from ESRD patients.

As our methodology is designed to use low sample volume, majority of the eight features are unidentified metabolites, where 5/8 features are large molecular weight species (>500 *m/z*) corresponding to ranges where lipids are usually detected. Based on matching *m/z* and tandem mass spectrometry experiments (Supporting Information, Ref. [5]), one of the features that can be tentatively assigned is *m/z* 239.20. This analyte is 2× higher on average in healthy donors and likely corresponds to a 15-carbon long fatty acid with 1 double bond (Figure 4b). The tentative assignment reflects that tandem mass spectrometry does not enable the inference of the double bond's placement, and this molecule was not detected in our HILIC-MS data. As this unsaturated fatty acid has not been reported before as a marker of ESRD in sweat, our analysis highlights that our methodology can select disease-related sweat markers. All selected model *m/z* fragments and the corresponding coefficients are included in Figure S19.

As training a separate lasso model among ESRD donors to identify analytes that are associated with length of time on dialysis returned a null model, we anticipate that lasso-selected sweat analytes are signatures shared across all ESRD donors in this cohort.

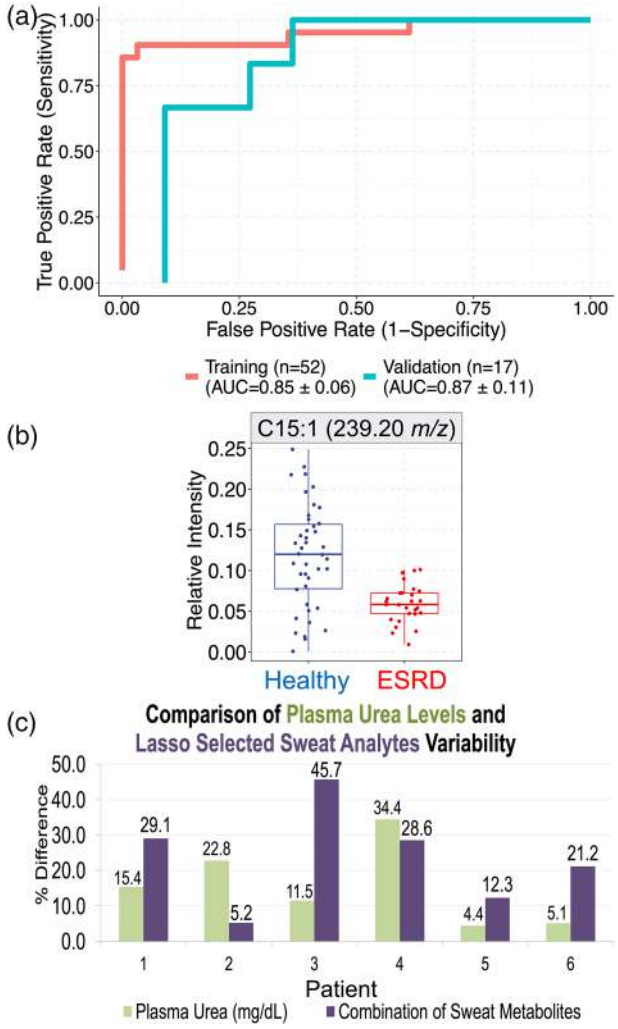


**FIGURE 4** (a) Receiver operating characteristic curves show the diagnostic performance of the lasso model on both training ($n = 52$ patients) and validation ($n = 17$ patients) sets in distinguishing between healthy and end-stage renal disease (ESRD) samples. (b) One of the eight lasso-selected analytes that can be tentatively identified as C15:1 (*m/z* 239.20) is 2× higher on average in healthy donors. (c) Comparisons of variability in plasma urea levels and predicted probabilities from lasso-selected sweat analytes for six ESRD donors from whom replicate samples were obtained 6 months apart pre-dialysis

Due to differences in clinical characteristics between healthy and ESRD patients, where 41% of healthy and 94% of ESRD patients are male, we compared the lasso-predicted probabilities between groups, while accounting for age and gender (Figure S22). As shown in Figure S22, the predicted probabilities do not notably change across ages and genders within the same patient group. Therefore, we infer that the signatures captured by the model do not simply reflect differences in age or gender.

Additionally, we compared the percent difference in clinical plasma urea levels and lasso-predicted probabilities for six ESRD patients (Figure 4c). Because sweat samples were collected from the same ESRD donors pre-dialysis 6 months apart, our comparisons shed light

on the model's prediction stability for these same donors. Although the percent differences in plasma urea levels for the same donors range from 4.4% to 34.4% with an average of 15.6%, the lasso-predicted probabilities range from 5.2% to 45.7% with an average of 23.7%. Moreover, we observe that the lasso-predicted probabilities have lower variability compared to the plasma urea levels for patients 2 and 4 (Figure 4c). Based on this comparison and data showing the predicted probabilities are not associated with gender or age, these results suggest that this methodology can yield stable markers with similar variability to currently used clinical markers.

## DISCUSSION

For the clinical realization of sweat-based diagnostics, an understanding of which metabolites are detected in sweat and how they change in the course of disease is needed. Using a combined mass spectrometry and machine learning methodology, our study, the first to look at sweat metabolites in the context of ESRD, demonstrates as a proof of concept that metabolic disturbances in ESRD can be detected in the sweat profile with 88.4% cross-validation accuracy and 0.85 AUC (52 sweat samples) and 82.4% accuracy and 0.87 AUC on a holdout test set (17 samples). The methodology has several key advantages, including the noninvasive, simple, and rapid sample collection, minimal sample preparation and ability to detect thousands of metabolites using DESI-MS, and the ability to focus on the important metabolites using lasso analysis even without knowing a priori their identities.

This work presents as a proof of concept whether healthy and ESRD patients exhibit any significant differences that can be detected in perspiration samples. For clinical use, one appropriate use case may involve an early detection of chronic kidney disease onset, especially as a microvascular complication from diabetes.[30] Multiple studies have probed metabolic differences related to chronic kidney progression using serum or urine metabolomics,[30–35] and we highlight some of the differences with our work. First, our work highlights that differences in serum metabolic profiles are not necessarily reflected in sweat. Although different studies[30,34,31] report large changes in taurine metabolism that can capture CKD progression, we find low levels of taurine ($m/z$ 124.00) (Figure S23) detected in sweat and minimal differences between healthy and ESRD donors.

In comparison, we find significantly higher concentrations of fatty acids. Our findings showing aberrations in fatty acid levels are consistent with published studies[30,31] that reported differences in acetylcarnitine levels and their association with clinical parameters in CKD (e.g., eGFR). More specifically, Hirakawa et al.,[32] which characterizes plasma- and urine-derived metabolites for predicting chronic kidney disease progression, identifies FA(15:1) as one of the features selected in their machine learning analysis. Although our lasso analysis is the first to select FA(15:1) as a sweat-based marker for ESRD using an unbiased methodology, the consistency in results suggests that the variance in these metabolite levels in sweat may help predict CKD progression. Moreover, although serum studies report[31] elevated palmitic acid levels are associated with CKD onset, our results show the suppression of palmitic acid in ESRD sweat, underscoring that serum metabolic changes are not always positively correlated with metabolic changes found in sweat.

An important finding from our study is the elevation of uric acid levels in sweat, and multiple studies report aberrations in the same pathway in both urine and plasma samples, including increases in xanthine[32] and xanthosine.[32,35] Although previous studies from our group and others have reported urea and uric acid changes in sweat,[5,36] our study uniquely probes how dynamic is the sweat metabolome in a disease context, particularly in ESRD. On one hand, we find that suppressed fatty acid levels in ESRD donors, when compared to healthy controls, are maintained after dialysis and do not change upon length of time on dialysis. These results suggest that the ESRD imposes longer term changes to fatty acid levels, consistent with dysregulated inflammatory lipid signaling as a known hallmark of ESRD.[20] In contrast, we find that changes in uric acid levels can be captured using our methodology, based on comparing samples' pre- and post-dialysis. Together, these results raise questions as to which solutes partition in sweat and what shapes their kinetics for developing robust markers of physiological health. Along these lines, the mechanism by which metabolic differences appear in ESRD versus healthy patients is not clear. It is possible that these results can be ascribed to differences in analyte filtration by the kidney, microvascular complications from diabetes, or both. Regardless of mechanism, these results suggest a substantial difference in human perspiration samples of ESRD patients.

As the precision health paradigm teaches us that deviations from an individually defined healthy baseline are informative for predicting disease, our combined methodology fits well within this theme. Specifically, tracking the sweat metabolome provides new opportunities to define a healthy baseline and to identify changes, such as the fatty acid differences reported in this study, which may act as useful early markers of disease. Moreover, we find that the selected markers by our statistical methodology do not significantly change across age, and gender, and they have variability on-par with clinical markers of kidney function, suggesting the viability of this methodology for clinical use. More generally, these results suggest that tracking aberrations in sweat metabolites may help enable new opportunities in precision health.

### AUTHOR CONTRIBUTIONS

*Data curation; formal analysis; investigation; methodology; writing—original draft*: Vishnu Shankar. *Investigation; project administration*: Basil Michael. *Investigation; methodology; project administration*: Alessandra Celli. *Conceptualization; investigation; methodology*: Zhenpeng Zhou. *Investigation; methodology; project administration*: Melanie D. Ashland. *Formal analysis; methodology; project administration; validation*: Robert Tibshirani. *Funding acquisition; project administration; supervision; writing—review and editing*: Michael Snyder.

### ACKNOWLEDGMENTS

VS acknowledges the Precision Health & Integrated Diagnostics Center seed grant. We also acknowledge support from the Air Force Office of Scientific Research through the Multidisciplinary

University Research Initiative (MURI) program (AFOSR FA9550-21-1-0170) and the National Institutes of Health (grant no. U54DK10255603, 5RM1HG00773508). We express our gratitude to Dr. Tammy Sirich of the Veterans Affairs Palo Alto Health Care System and Stanford Nephrology Division for obtaining sweat samples from end-stage renal disease patients and providing important feedback on the manuscript.

## CONFLICTS OF INTEREST

Richard N. Zare, who is an author of the manuscript, is a member of the Advisory Board and was not involved at the handling of the peer-review process of this submission. All authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

De-identified sweat data for this study are available at https://osf.io/mh2gk/?view_only=b4a33a69a09248f1be4f3571bb6a8074. Source code for processing raw data is found at https://zarelab.com/research/massexplorer-a-tool-to-help-guide-analysis-of-mass-spectrometry-samples/.

## ETHICS STATEMENT

Sample collection was approved by the Institutional Review Boards of Stanford University and Santa Clara Valley Medical Center. Informed consent was obtained from all participants prior to sample collection.

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## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/ntls.20220048.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Shankar V, Michael B, Celli A, et al. Identification of end-stage renal disease metabolic signatures from human perspiration. *Nat Sci*. 2022;1-9. https://doi.org/10.1002/ntls.20220048