Hemodialysis Treatment Time: A Fresh Perspective

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Summary
Historical, clinical, economic, and technological developments have driven a shift in clinical practice from predominantly 6-hour-long hemodialysis treatments to much shorter treatment times that are prevalent today. Patients, physicians, and providers had considered shortening dialysis treatments as a means to decrease the overall burden imposed by this necessary life-saving therapy. However, shorter dialysis is not a panacea and may engender trade-offs in terms of patient morbidity and mortality. We examine the literature with the benefit of hindsight and in light of recent studies that have improved understanding of the complex relationship between dialysis dose and outcome. We touch upon the role of dialysis frequency relative to treatment time. We conclude with the suggestion that a new treatment paradigm should consider a minimum adequate dialysis treatment time of 4 hours for the majority of patients, with anything shorter becoming the exception rather than the rule.


Introduction
In the over 40 years since hemodialysis has become widely available in the United States, the pendulum has swung from predominantly long (6 + hours) to more efficient, but shorter (<4 hours) and experimentally ultrashort (<2 hours) periods and has now begun to rebound toward longer treatments of 4 + hours, driven by historical, clinical, economic, and technological developments (Figure 1). Patients, physicians, and providers had considered shortening TT as a means to decrease the overall burden imposed by this life-saving therapy. However, shorter TT is not a panacea, and may engender trade-offs in terms of patient morbidity and mortality. We examine dialysis TT within the historical context and evolution of clinical practice, with the benefit of hindsight as well as in light of recent studies that have improved our understanding of the complex relationship between dialysis dose and outcome.

The Kiil and Twin Coil dialyzers commonly used in the 1960s and early 1970s were characterized by small diffusive surface area, impermeate cellulosic membranes, and/or open recirculating dialysate reservoirs and generally necessitated at least 6 hours of therapy three times per week (1–4). The average patient dialyzed for 18 h/wk, extrapolating to 936 hours on dialysis annually even allowing for 20% missed treatments, which is equivalent to 1 month of every year tethered to the dialysis machine. This estimate ignored patient commute and “wait” times, which were not inconsequential in that era, considering the need to blend individualized dialysate and manually set up equipment, along with a paucity of conveniently located dialysis facilities. Therefore, much of the drive to reduce treatment times (TTs) was related to the desire of patients to spend less time on the dialysis machine.

Motivation to reduce TT was also fueled by the belief that providing shorter, more efficient dialysis treatments could be performed safely while being cost-effective. The Medicare entitlement (section 2991 of PL92-603, Social Security Amendments, 1972) was enacted to enable widespread provision of life-saving maintenance dialysis treatments, the costs of which were beyond the means of most Americans. Over its evolution, the program resulted in: (1) more patients on dialysis than initially projected; (2) disproportionately greater allocation of healthcare dollars for one relatively small segment of society; (3) predominantly facility-based outpatient treatment with strategic programmatic cost-shifting toward clinical management to keep costs steady; and (4) a second-order signal to manufacturers and suppliers to compete for market share through cost-reducing technical innovations (5).

To maintain financial viability of the program, some degree of cost containment was necessary. This was largely accomplished through composite rate payments (i.e., capitated payment for dialysis treatment and related routine laboratory tests) made to dialysis facilities, which promoted cost-conscious care delivery. In effect, a “cost-shifting” occurred where the onus for keeping cost of dialytic therapy within the capitated composite rate payments fell on dialysis providers. Because there was minimal adjustment of the composite rate over the next two decades, this necessitated improved efficiency just to keep up with inflation.

Shorter TT that met requirements for solute and fluid removal were deemed to be achievable with improved dialysis efficiency. There was a belief that the additional cost of technological advancements required to achieve maximal dialytic efficiency will outweigh the growth of expenses from infrastructure investments and labor that were required as the dial-

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ysis population expanded. An alignment of objectives emerged between patient interests to decrease the time burden of therapy, physician interests to provide the least burdensome effective therapy, and advantages for more efficient care delivery brought about by shorter dialysis treatments. Therefore, there existed an economic incentive to motivate continued research and development to enhance dialysis efficiency.

Enhancing Dialysis Efficiency

Barriers to shortening TT were overcome one by one through innovative refinements to dialyzer membrane design that enhanced diffusive permeability, improved engineering of dialysis delivery equipment, and made modifications to dialysate composition. The major objective was to increase dialytic capacity for solute clearance (primarily measured in terms of urea removal) so as to maintain the same total clearance over less time. The hollow fiber dialyzer design allowed for a compact, more efficient use of surface area to maximize diffusion (6,7). Membrane materials evolved from basic cellulose into cuprophane and then semisynthetic and fully synthetic fibers that allowed for enhanced diffusive clearance as well as greater convective solute and fluid flux (8). The enhanced capacity for fluid removal necessitated precise control of ultrafiltration rate, spurring the development of blood pumps and volumetric ultrafiltration (4,9).

As the permeability of dialyzers increased, diffusion of dialysate components back into the blood compartment was also enhanced. Serum bicarbonate diffused out to the dialysate, whereas the acetate buffer in dialysate entered the bloodstream at rates that sometimes exceeded patients’ metabolic capacity to convert it into bicarbonate, leading to hypoxia and vascular instability (10,11). Thus, transition to bicarbonate-buffered solutions also spurred newer hemodialysis (HD) machines with more sophisticated dialysate proportioning systems, and in parallel, outpatient clinic design evolved to allow for central delivery of bicarbonate solution (12,13).

Clearance Trumps Time

By the late 1970s, many small short-term, single-center case series reported equivalent metabolic intermediate outcomes between conventional long duration and shorter (<4-hour TT) HD in small patient samples, utilizing increasingly sophisticated technologies (14–18). Nonetheless, some patients did experience hypotension, neuropathy, and difficulties with fluid removal, and some facilities noted the higher costs of the required equipment (19–22). As equipoise was established between proponents of long versus short TT, the first multi-center large study of dialysis adequacy was funded by the National Institutes of Health (NIH). The National Cooperative Dialysis Study (NCDS) compared outcomes among patients randomized to one each of two levels of dialysis clearance (i.e., high/low urea level) and TT (short/long) using a 2×2 factorial design. The NCDS concluded that patients with “low time averaged blood urea nitrogen concentrations” experienced fewer treatment withdrawals and hospitalizations than patients with higher levels (23). There was no statistically significant difference between long and short TT; however, longer time approached borderline significance (P = 0.056) with regard to reduced hospitalization and complication rates. The study was not powered to examine differences in mortality. On the basis of these findings, many physicians concluded that dialysis dose on the basis of urea kinetics, which was formalized into the Kt/V metric (urea clearance time product divided by its volume of distribution) after a kinetic reassessment of the results of the NCDS (24). Confidence in this approach was reinforced by several

Figure 1. Timeline of the evolution of dialytic treatment time and associated events. TT, treatment time; BU, blood urea; URR, urea reduction ratio; NCDS, National Cooperative Dialysis Study; HFN, Frequent Hemodialysis Network; PPS, prospective payment system; HEMO Study, Hemodialysis Study.
survival studies demonstrating similar outcomes between longer TT and short TT using high efficiency and/or high flux membranes (13,25,26).

Then There Was Doubt

Nevertheless, not all clinicians in the United States were convinced that shorter TT was appropriate for all patients. After all, whereas the average TT declined in the United States, the dialysis program in Tassin, France, maintained long, 8-hour overnight dialysis thrice per week with exemplary results that were linked to optimal fluid management and BP control (27). In the United States, improvements in health-related quality of life and biochemical profiles seen during this period were interpreted by some as further justification of the urea-centric paradigm of dialytic titration. In retrospect, however, these improvements may likely have resulted from factors other than dialytic titration, such as trends toward the following: use of biocompatible membranes that decreased immune activation and possibly intradialytic symptoms (28–30), dialysis equipment capable of precise dialysate delivery and tightly controlled fluid removal (4,9), bicarbonate-based in lieu of acetate-based dialysate (10,31), better control of hyperparathyroidism and management of renal osteodystrophy caused by widespread use of activated vitamin D analogs (32–35), and escalating use of erythropoietin (36).

Data from a national cohort from 1986 indicated that TT of <3.5 hours was associated with greater mortality compared with patients treated with longer dialysis (37). Compounding the issue, because the mean TT had fallen to almost 3 hours during 1986 to 1987, 53% of patients were concurrently prescribed an inadequate Kt/V <1.0 (38). More important, critics highlighted that mortality rates in the United States during the period 1982 to 1987 were found to be higher than in Europe and Japan (39). It was further demonstrated that the prescribed dose of dialysis was higher in Europe than the United States (40). These concerns were summarized in a national meeting addressing this issue (Dallas Morbidity, Mortality, and Prescription of Dialysis Symposium) in 1989, which precipitated a re-examination of what constituted adequate dialysis (41). The potential role of TT relative to dialysis adequacy and outcomes formed part of the discussions within the renal community during this period. However, urea kinetics once again took a front seat, and at the close of the decade, there were more reports of single-center experiences with favorable outcomes associated with short but “adequately dosed” dialysis treatments (42–44).

The Next Hemodialysis Outcome Study

In the midst of renewed concern about dialysis adequacy, better relative survival was observed in the subpopulation of American patients whose delivered dialysis dose was above Kt/V of 1.2, further reinforcing interest in urea-based dialytic titration and prompting a renewed search for the minimum standard for “adequate dialysis dose” (45,46). A new equipoise led to the second large NIH-funded randomized clinical trial on HD outcomes, the Hemodialysis (HEMO) Study. This trial used equilibrated Kt/V (eKt/V [47,48]) as the metric by which HD dose was assessed and titrated to account for “urea rebound” (i.e., increased blood concentration of urea over the succeeding 20 to 30 minutes after dialysis is completed) resulting from solute and fluid movement between tissue compartments and the interstitial and vascular compartments (49–51). The HEMO study compared high urea clearance (eKt/V of 1.45) to conventional clearance (eKt/V of 1.05; analogous to single pool Kt/V of approximately 1.2) and found no significant difference in mortality or hospitalization after a mean follow-up of 2.8 years (52). The 2 × 2 factorial study design likewise showed no outcome differences between low versus high flux dialyzers, except in the subgroup with vintage >3.7 years.

The HEMO study bears relevance on the consideration of the effects on survival in two ways. First, the higher eKt/V group was dialyzed on average for longer than the lower eKt/V group; in this light, an absent effect of greater eKt/V on mortality might be taken to signal no effect of treatment time. Second, the association between treatment time per se and mortality was examined in the pooled cohort, again with no association detected. Cautious interpretation is advised, however. Within each eKt/V group, treatment time assigned as “the shortest…consistent with the patient’s assigned dose.” Thereby, larger patients would be assigned to longer treatment times than smaller patients, which might have biased estimates in favor of longer treatment times. Conversely, less favorable access types (e.g., catheters, arteriovenous accesses in patients with poor vascular health) would promote longer treatment times, and thereby estimates would favor shorter treatment times. The net effects of these biases cannot be known. However, it is incontrovertible that session length was not assigned randomly (even within the HEMO study), and therefore such confounding cannot be ignored. For this reason, HEMO was not a randomized trial of session length, and analyses of treatment time therein were subject to all of the same biases as in any observational study. In addition, data from the HEMO study likely generalized less to the overall dialysis population considering the stringent inclusion criteria.

Rationale for Renewed Interest in Treatment Time

Among components of the dialysis prescription, TT is likely most influential with regard to middle or larger molecule clearance (53). Although dialyzer flux plays a contributory role in cleansing the vascular fluid, transfer of molecules across from the intracellular fluid to the interstitial fluid and into the vascular fluid plays an important role in total body clearance (54). With contemporary equipment and high flux membranes, one can efficiently cleanse the vascular compartment. However, whole body clearance requires that solutes re-equilibrate from deeper reservoirs, so as to be available for dialytic removal. Intercompartmental (e.g., intracellular to extracellular) redistribution is typically much slower for larger molecules. Thus, despite their efficient dialytic removal from the blood, total body clearance is greatly reduced with shorter TTs (55,56).

The movement of sodium and water across body compartments has been less well studied. This consideration may be important in understanding why recent observational studies have suggested that longer TT is favorably
associated with morbidity and mortality (Table 1) (27,37,57,58). The ability to ultrafilter very large volumes is limited (hemodynamically) by the rate at which salt and water re-equilibrate across body compartments (59). Increased concentrations of sodium in the dialysate ameliorates hemodynamic responses to dialysis treatments, promoting thirst, increased fluid intake, and increased predialysis BP (62,63). A cycle of increased fluid gain followed by an increased rate of fluid removal within the same TT, in part to attain BP targets, predisposes patients to suffer from intradialytic hypotension (64–66).

Recently, both intradialytic hypotension and high ultrafiltration rates have been linked to mortality risk in dialysis patients (67–71). It has been demonstrated that longer dialysis with slower ultrafiltration rates allows greater salt and water removal from patients without inducing profound hypotensive episodes (72–74). Long overnight or nocturnal dialysis performed thrice per week for patients with a history of frequent and large interdialytic fluid gains (unresponsive to conventional “short” treatments) improves BP and fluid control (75,76). Thus, longer TT with slower rates of ultrafiltration and with lower dialysate sodium may be an important contributor to both wellbeing and survival in dialysis patients.

Finally, the highly efficient dialysis prescription requires that a large volume of blood is cleansed within short TTs. By design, rapid blood transport occurs through the dialysis circuit, necessitating that high blood-flow rates be drawn from and subsequently returned through the vascular access. Such demand may take its toll on the arteriovenous vascular access endothelium, which may adversely affect both access maturation and patency. Many Asian and European countries that use slow dialysis (and thereby lower blood-flow rates) have greater utilization of arteriovenous accesses among prevalent and incident patients as well as shorter times to maturation and higher maturation rates than the U.S. (77,78). Notwithstanding that some of these regional differences are likely explained by ambient vascular health and patient behaviors, it is plausible that high blood-flow requirements (with the requisite hemodynamic and shear stress) may contribute to poor vascular access maturation and survival. It is also likely that attempts to perform very rapid HD place unrealistic (or even unnecessary) expectations on what constitutes a “mature” or functional access (79–82). Therefore, speculating further, the short TT dialysis prescriptions may select for circumstances that disadvantageously promote catheter exposure and thereby further compromise patient survival.

Re-evaluating Outcomes Associated with Treatment Time

Despite a relatively narrow range of TT (majority between 3 and 4.5 hours, with the exception of nocturnal dialysis), recent observational studies have demonstrated relative greater comparative survival and less hospitalization with longer dialysis three times a week (69,83–86). Data from the United States, Europe, and Japan where the majority of patients dialyzed for <4 hours, indicated that beyond Kt/V, TT of >4 hours was significantly associated with lower adjusted relative risk of death (0.81, P = 0.0005) (69). Because Japanese reimbursement policy favors longer (>4 hours) TT in all but the sickest patients, it is important to note that the association between TT and survival was observed within the European and U.S. subgroups. In Australia and New Zealand, where the largest group of patients dialyzed between 4 and 4.4 hours, TT of >4.5 hours was similarly associated with reduced death risk, as TT of 4.5 to 4.9 hours had adjusted hazard ratios (HR) for mortality of 0.80 (P < 0.05) (84). In a large prevalent cohort of American patients with mean Kt/V of 1.6, an adjusted HR of 1.12 (with confidence limits of 1.06 and 1.18, inferred from Figure 3 in reference 85) was observed in patients with TT of >2.5 to 3 hours compared with those with TT of 3.5 to <4 hours. In an incident U.S. cohort that survived for at least 30 days, increased death risk was associated with TT of <4 hours (86). Utilizing marginal structural models to account for time-dependent confounding, the adjusted HR was 1.42 (P < 0.0001) for TT of <4 hours relative to TT of ≥4 hours. Importantly, this association was unchanged in the subgroup of patients whose eKt/V was >1.2, suggesting an influence of TT independent of optimal urea kinetics. It is worth noting that each of the above analyses were adjusted for some index of body size.

Finally, in a cohort of patients dialyzed three times per week, a matched analysis comparing TT of 4 to 8 hours showed the latter group to have better survival (HR = 0.28, P = 0.02) along with fewer hospitalizations, regression of left ventricular mass, better cognition, and better biochemical indices (87). Similarly, preliminary data presented by Lacson et al. (88) at the 2010 National Kidney Foundation meeting corroborates better survival with 8 hours of in-center nocturnal HD relative to a propensity score matched control group on conventional HD with mean TT of 3.5 to 4 hours with HR = 0.66 (P = 0.002). These observational studies do not prove causation and are all subject to residual confounding. Moreover, comparisons between 3.5 to 4- and 8-hour treatments bear different clinical significance (because of logistical considerations related to implementation) than do comparisons between <4- and ≥4-hour treatments. However, the latter data do provide support for the underlying physiologic principle that longer treatment times may be better.

Hemodialysis Frequency versus Time

Much of the focus of dialysis adequacy after negative results from the HEMO study has been on increasing the frequency of dialysis treatment. The NIH-funded Frequent Hemodialysis Network (FHN) recently published the results of the short daily HD randomized trial demonstrating significantly better composite outcomes (change in left ventricular mass or death and change in physical component score or death) for six versus three times per week HD with TT at 2.5 ± 0.3 hours versus 3.5 ± 0.6 hours per treatment, respectively (89). The total weekly time for the short daily treatments was ~15 hours versus approximately 10.5 hours for the controls. It can be argued that
<table>
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<tr>
<th>Population Studied</th>
<th>Reference or Control Group</th>
<th>Long Treatment Time Group</th>
<th>Results for Longer Hemodialysis Treatment Time (Adjusted Models)</th>
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<tr>
<td>Incident HD patients</td>
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<tr>
<td>Australia and New Zealand (84)</td>
<td>TT = 4.0 to 4.4 hours (n = 2,091)</td>
<td>TT = 4.5 to 4.9 hours (n = 753)</td>
<td>20% lower relative risk of death&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>United States (86)</td>
<td>TT &lt;4 hours</td>
<td>TT ≥ 4 hours</td>
<td>Shorter treatment time has 42% greater death risk (longer time as reference)&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Prevalent HD patients</td>
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<tr>
<td>International (DOPPS) (69)</td>
<td>TT ≤4 hours (n = 14,353)</td>
<td>TT &gt; 4 hours (n = 1980)</td>
<td>19% lower relative risk of death&lt;sup&gt;c&lt;/sup&gt; and 16% lower cardiopulmonary death risk&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>United States (85)</td>
<td>TT = &gt;2.5 to 3.0 hours (n = 4889)</td>
<td>TT = 3.5 to &lt;4.0 hours (n = 29,744)</td>
<td>Shorter treatment time has 12% greater relative death risk (longer time as reference)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>United States (76)</td>
<td>TT = 3.7 ± 0.5 hours (n = 15,334)</td>
<td>TT = 7.9 ± 0.5 hours (n = 655)</td>
<td>12% lower hospitalization risk for all causes&lt;sup&gt;b&lt;/sup&gt; (31% better death risk before adjustment, not significant after case-mix + lab adjustment)</td>
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<tr>
<td>Turkey (87)</td>
<td>TT = 4 hours (n = 247)</td>
<td>TT = 8 hours (n = 247)</td>
<td>68% lower death risk&lt;sup&gt;e&lt;/sup&gt;; fewer hospital days: 5.43 &lt;i&gt;versus&lt;/i&gt; 18.78 days/1000 dialysis treatments&lt;sup&gt;e&lt;/sup&gt;</td>
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HD, hemodialysis; TT, treatment time.

<sup>a</sup><sup>P</sup> < 0.05.

<sup>b</sup><sup>p</sup> < 0.0001.

<sup>c</sup><sup>P</sup> = 0.0005.

<sup>d</sup><sup>p</sup> = not stated, but confidence interval estimated at 1.06, 1.18 from the figure.

<sup>e</sup><sup>P</sup> = 0.002.
increasing frequency is just another dimension of increasing total time on dialysis. However, there may be a threshold whereby increasing dialysis frequency even up to five to seven times per week can be offset by ultrashort dialysis time. For example, in one observational study, there was a graded increase in survival among patients undergoing frequent HD to total weekly times of <12, 13 to 15, and >15 hours (90).

Results from the FHN frequent nocturnal hemodialysis trial have not been published. Despite the expectation of even better outcomes because of improvements in the composite outcome of mortality and major morbidity (acute myocardial infarction or stroke) in a recent observational study (91), FHN investigators were unable to meet their original enrolment targets because of unexpected challenges (92). Nevertheless, results of observational studies from home nocturnal HD programs such as that in Toronto, Canada, and Lynchburg, Virginia, indicated significant patient well being with lower requirement for antihypertensive medications, phosphate binders, and erythropoietin in dialysis occurring overnight six to seven times per week (93–96). Preliminary experience from Hong Kong indicates that conversion to every other night long 8-hour dialysis had similar results, with decreased antihypertensive medications, phosphate binder requirements, and erythropoietin dose along with improved well being (97). The Tassin experience already exhibits similar improvements with long thrice weekly HD (27,98). Similarly, favorable changes in wellbeing and medications can also be achieved with thrice weekly in-center long nocturnal HD (75,99,100).

Differentiating the effect of TT versus increasing the frequency of HD beyond three times per week may be a more challenging clinical issue. Furthermore, the cost benefit of longer versus more frequent dialysis must be further evaluated. In the past there were limited numbers of dialysis facilities and dialysis stations; thus, rapid turnover of dialysis stations was necessary to accommodate all of the patients with end-stage renal disease. This is no longer a major constraint in the United States and most developed countries in that there are sufficient stations so that patients can potentially have longer dialysis treatments. In-center accommodation of long nocturnal patients still presents challenges (101), but they are not insurmountable. Logistically, scheduling patients for more frequent treatments, even during the day, is the greater challenge for providers. In addition, there remains reluctance on the part of patients to increase either TT or frequency of dialysis. Most patients desire to dialyze with the minimum “necessary” frequency and TT (either at home or in center), express fears regarding their ability for self-care, and are lacking critical information toward making informed decisions about their dialytic care. Education for patients with respect to individual skill, resources, technical requirements, and benefits associated with adoption of either longer or more frequent dialysis is essential to overcoming this limitation (92,102,103).

Moving Forward

Although it is becoming clear that better clinical outcomes can be anticipated with longer or more frequent hemodialysis, overall costs savings remains speculative until hospitalization rates and days in hospital are included in the economic model of dialysis. The new prospective payment system for dialysis services does not include inpatient costs (104). In the setting of capitation or accountable care organization-type plans, the cost benefit of increased dialysis time and frequency will become more apparent (105–107). Systemic changes associated with these types of patient-centered care systems will include a blurring in the division between reimbursement for outpatient care and for inpatient care, such as the current separation between Medicare Part A and Part B. The hope is for greater emphasis on pre-emptive care that may incur additional expenses upfront but may decrease hospitalization-associated costs down the road. In the interim, inadequate short dialysis treatments likely lead to complications, increased hospitalization, and decreased survival and may have a negative effect on the total cost of therapy. We suggest that in the setting of three-times-per-week HD, a new minimum adequacy prescription target can be established by physicians to include specifications for TT ≥4 hours, with anything less becoming the exception rather than the rule.

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Disclosures

Dr. Lacson is a full time employee of Fresenius Medical Care, North America. Dr. Brunelli serves on medical advisory boards to C.B. Fleet Co. and Amgen, and his spouse is an employee at AstraZeneca. Statements in the manuscript represent opinions of the authors and do not necessarily represent an official position of their respective institutions.

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