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Research paper

Do clinicians follow heuristics in prescribing antidepressants?

Isaac Lage [a], Melanie F. Pradier [a], Thomas H. McCoy Jr [b,c], Roy H. Perlis [b,c,*], Finale Doshi-Velez [a,**]

[a] Harvard John A. Paulson School of Engineering and Applied Sciences, 29 Oxford Street, Cambridge, MA 02138, USA
[b] Center for Quantitative Health, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114, USA
[c] Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA

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ABSTRACT

Background: While clinicians commonly learn heuristics to guide antidepressant treatment selection, surveys suggest real-world prescribing practices vary widely. We aimed to determine the extent to which antidepressant prescriptions were consistent with commonly-advocated heuristics for treatment selection.
Methods: This retrospective longitudinal cohort study examined electronic health records from psychiatry and non-psychiatry practice networks affiliated with two large academic medical centers between March 2008 and December 2017. Patients included 45,955 individuals with a major depressive disorder or depressive disorder not otherwise specified diagnosis who were prescribed at least one of 11 common antidepressant medications. Specific clinical features that may impact prescribing choices were extracted from coded data, and analyzed for association with index prescription in logistic regression models adjusted for sociodemographic variables and provider type.
Results: Multiple clinical features yielded 10% or greater change in odds of prescribing, including overweight and underweight status and sexual dysfunction. These heuristics were generally applied similarly across hospital systems and psychiatrist and non-psychiatrist providers.
Limitations: These analyses rely on coded clinical data, which is likely to substantially underestimate prevalence of particular clinical features. Additionally, numerous other features that may impact prescribing choices are not able to be modeled.
Conclusion: Our results confirm the hypothesis that clinicians apply heuristics on the basis of clinical features to guide antidepressant prescribing, although the magnitude of these effects is modest, suggesting other patient- or clinician-level factors have larger effects.
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1. Introduction

Outpatient management of major depressive disorder exhibits substantial variation in practice, whether measured by clinician survey (Goldberg et al., 2015; Nakagawa et al., 2015) or descriptive analysis of large clinical data sets (Abbing-Karahagopian et al., 2014; Pradier et al., 2020).

In part, this variability likely reflects differences in medical education as well as exposure to practice guidelines and algorithms (Kavanagh et al., 2017). For example, practices learned during residency are likely to be continued during subsequent clinical practice (Epstein et al., 2013). Certain heuristics are well-known to most psychiatrists - for example, the use of more activating versus more sedating medications - even in the absence of strong evidence to support their utility (Lin and Stevens, 2014; Papakostas and Larsen, 2011).

In the present study, we sought to determine the extent to which clinicians adhere to heuristics, explicitly or implicitly, in antidepressant treatment selection. As interest grows in enhancing prescribing with the introduction of biomarkers or decision support tools, understanding how clinicians currently make decisions only grows in importance. That

* Correspondence to: R. H. Perlis, Massachusetts General Hospital, 185 Cambridge Street, 6th Floor, Boston, MA 02114, USA.
** Correspondence to: F. Doshi-Velez, Harvard University, 150 Western Ave, 2.336, Allston, MA 02134, USA.
E-mail addresses: rperlis@mgh.harvard.edu (R.H. Perlis), finale@seas.harvard.edu (F. Doshi-Velez).

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is, understanding clinician decision making at baseline will facilitate incorporation of new decision supports, particularly if those recommendations conflict with established heuristics.

We curated a small set of common prescribing heuristics - i.e., relative indications or contraindications - on the basis of comorbid illness features in major depressive disorder detectable on the basis of coded clinical data. Some of these were related to safety (risk for QT prolongation, e.g.) whereas others targeted tolerability and acceptability (weight gain or loss, e.g.). We sought to understand, first, the extent to which clinicians appeared to behave according to these heuristics - that is, whether their prescribing differed when a feature was present. We then investigated differences between practice in two settings: specialty psychiatry, and non-psychiatry - to understand whether different clinical specialties might apply these rules more or less often.

2. Methods

2.1. Study overview and cohort description

We identified 73,736 individuals age 18–80 years drawn from the outpatient clinical networks of two academic medical centers in Eastern Massachusetts that share an electronic health record system. These networks are referred to subsequently as Site A (45,955 patients) and Site B (27,781 patients). All patients had received at least one electronically-prescribed antidepressant from among the most commonly-prescribed between October 2008 and December 2017 with a diagnosis of MDD (International Classification of Diseases, Ninth Revision (ICD9) codes 296.2×, 296.3×) or depressive disorder not otherwise specified (311) at the nearest visit to that prescription. We generated a data mart with variables extracted from electronic health records of these two health systems using i2b2 server software (i2b2, Boston, MA, USA) (Murphy and Wilcox, 2014, p. 2). Available patient data included sociodemographic and insurance information, diagnostic and procedure codes, as well as inpatient medication administrations and outpatient medication electronic prescriptions. Prescriber type (psychiatrist versus non-psychiatrist) was defined based on the recorded specialty of the physician writing the antidepressant prescription. The study protocol was approved by the Massachusetts General -Brigham institutional review board, waiving the requirement for informed consent as only de-identified data were utilized and no human subjects contact was required.

2.2. Clinical heuristic definition

Two academic psychopharmacologists (RHP, THM) curated heuristics for antidepressant prescribing on the basis of safety and tolerability. Each heuristic is of the form, 'when [clinical feature] is present, you should [avoid/promote] [specific antidepressants], where that feature must be identifiable on the basis of an ICD9 or 10 diagnostic code. The expert clinicians incorporated principles embodied in standard European, Canadian, and American treatment guidelines as well as physician reference materials, most notably UpToDate and a large continuing medical education psychopharmacology course(Kennedy et al., 2016; National Guideline, 2010; Rush et al., 2020). In general, these heuristics correspond closely to other published guidance (Alonso-Pedrero et al., 2019; Blumenthal et al., 2014; Castro et al., 2013; "Chance of side effects with certain antidepressant medicines," n.d.; Henry, 1997; Schneeweiss et al., 2010; Stone et al., 2009). We considered antidepressant prescribing heuristics for patients with 10 different clinical features consisting of comorbid diagnoses and symptoms (see Table 1) for the list of conditions and the number of patients with each condition). The medications to be avoided or promoted for each condition are listed in Table 2. Symptoms and comorbidities were defined on the basis of ICD9/ICD10 diagnostic codes, CPT codes and medications (Supplemental Table 1). Patients with at least 1 of the associated codes are considered to exhibit the clinical feature (see Supplemental Table 2 in the supplement for a secondary analysis with the threshold set at 2 and 3 associated codes).

Table 1
Demographics.
Mean ± standard deviation for continuous variables and count - proportion of patients with binary variables for demographic variables and clinical features for all patients, for psychiatry patients and for non-psychiatry patients.

Variable	All patients	Psychiatry patients	Non-psychiatry patients
Age	47.52 ± 15.33	42.23 ± 15.31	48.16 ± 15.21
Gender: female	29,597–0.64	2655–0.54	26,942–0.66
Race: White	37,470–0.82	3916–0.8	33,554–0.82
Insurance: private	25,951–0.56	3110–0.63	22,841–0.56
Insurance: unknown	4221–0.09	259–0.05	3962–0.1
Provider: psychiatrist	4912–0.11	N/A	N/A
Anxiety	9542–0.21	1670–0.34	7872–0.19
Fatigue	8367–0.18	881–0.18	7486–0.18
Insomnia	7154–0.16	988–0.20	6166–0.15
Overweight	6756–0.15	605–0.12	6151–0.15
Underweight	2456–0.05	261–0.05	2195–0.05
Poor concentration	1671–0.04	433–0.09	1238–0.03
Sexual dysfunction	894–0.02	89–0.02	805–0.02
Nonadherence	790–0.02	141–0.03	649–0.02
Suicidality	235–0.01	70–0.01	165–0.00
QT prolongation	222–0.00	19–0.00	203–0.00

Table 2
Expert-curated heuristics adapted from standard guidelines and medical education programs.
The table reflects medications to be promoted (used more often) or avoided (used less often) among individual patients with the relevant characteristics, based on expert curation of selected heuristics from standard guidelines and medical education programs for antidepressant prescribing.

AVOID
QT prolongation: fluoxetine, citalopram, escitalopram
Nonadherence: paroxetine, venlafaxine, duloxetine
Sexual dysfunction: fluoxetine, sertraline, paroxetine, venlafaxine, citalopram, escitalopram, duloxetine
Overweight: mirtazapine
Poor concentration: paroxetine, mirtazapine
Suicidality: nortriptyline, amitriptyline, bupropion, venlafaxine, citalopram, duloxetine
Underweight: bupropion, fluoxetine, sertraline, venlafaxine, duloxetine

PROMOTE
Anxiety: sertraline, paroxetine, mirtazapine, citalopram, escitalopram
Nonadherence: fluoxetine
Sexual dysfunction: bupropion, mirtazapine
Fatigue: bupropion, fluoxetine, venlafaxine, duloxetine
Insomnia: sertraline, paroxetine, mirtazapine, citalopram, escitalopram
Overweight: bupropion
Poor concentration: bupropion
Underweight: mirtazapine

2.3. Rule matching

We considered only the index prescription for one of the 11 most-prescribed antidepressants during the study period - fluoxetine, citalopram, escitalopram, paroxetine, venlafaxine, duloxetine, sertraline, mirtazapine, bupropion, nortriptyline and amitriptyline - as a prescribing event. See Supplemental Fig. 1 for the distribution of antidepressant prescriptions across sites. To determine whether a prescribing event was consistent with a heuristic, we looked at all of an individual's coded clinical data in the 12 months prior to the prescribing event (see

Supplemental Table 3 in the supplement for a secondary analysis relaxing the restriction to consider all codes available in the EHR prior to the prescribing event, as well as in a 6 month window).

2.4. Analysis

We used logistic regression to test the association between presence or absence of each clinical feature and antidepressant prescriptions based on the curated prescribing heuristics. We ran an unadjusted analysis, and an analysis with models adjusted for sociodemographic features including age, gender (male/female), race (white/non-white), and insurance type (private/public/unknown). We also examined provider type (psychiatrist/non-psychiatrist). A secondary analysis included feature-by-provider type interaction, to determine whether features were differentially applied by one type of provider versus the other. The outcome variable was the presence or absence of a prescription that follows the heuristic, where "following a heuristic" refers to prescribing at least one promoted antidepressant, or no avoided antidepressants for promote/avoid rules respectively.

When reporting statistical significance, we use a significance threshold of 0.05 with a Bonferroni correction across all heuristics (this results in 15 comparisons and a threshold of 0.0033). We also indicate clinically meaningful effects (defined a priori) by setting a cutoff of odds-ratios larger than 1.1 or smaller than 0.9 conditioned on the term being statistically significant - i.e., odds are 10% increased or decreased.

We conducted our primary analyses on site A, holding out site B to explore consistency of results across health systems. Results thus pertain to the site A cohort unless otherwise specified.

3. Results

The site A cohort included 45,955 individuals, who were 64% female and 82% white, with a mean age of 47.52 [SD 15.33]; (Table 1). Clinical features among individuals treated in psychiatric and non-psychiatric settings are summarized in Table 1 as well.

Association between individual clinical features and prescribing, indicating consistency with one or more heuristics, is summarized in Table 3. The greatest difference in prescribing rates, among those heuristics significantly associated with prescribing, was observed for underweight-avoid (0.1), underweight-promote (0.08), and sexual dysfunction-avoid (0.07). Table 4 presents these analyses repeated for site B. Here, the greatest differences in prescribing rates were observed for underweight-avoid (0.16), sexual dysfunction-avoid (0.15), and underweight-promote (0.14). The underweight and sexual dysfunction heuristics, along with several others, show consistently large differences in prescribing behavior in both sites.

Our main analysis investigated the statistical and clinical significance of these results using a logistic regression analysis with heuristic following as the outcome. We first ran an unadjusted logistic regression, then one adjusted for condition-related and sociodemographic factors. See Table 3 for the odds ratios and 95% confidence intervals of the unadjusted analysis, and of the clinical feature and the interaction term between provider type and the clinical feature in the adjusted analysis. Clinical features have significant and clinically meaningful effects in 8 out of 15 heuristics in the unadjusted analysis and 7 out of the 15 heuristics in the adjusted analysis. Heuristics with significant and clinically meaningful effects in the adjusted analysis include 'avoid' heuristics for sexual dysfunction, overweight, underweight and 'promote' heuristics for: anxiety, fatigue, overweight, and underweight. The remaining clinical features do not have significant and clinically meaningful effects. The poor concentration-promote heuristic has a significant and clinically meaningful effect in the unadjusted analysis, but not the adjusted one (see Supplemental Table 4 for the odds ratios of all terms, and Supplemental Table 5 for the *p*-values and the coefficients). The results that follow reference only the adjusted analysis.

We replicated the logistic regression analysis in site B to determine whether our findings are generalizable, or are specific to a single health system. See Table 4 for the results. All of the statistically significant heuristics from site A remain significant in site B; the insomnia-promote and poor concentration-promote rules were significant in site B, but not A. (See Supplemental Table 6 for the demographics in site B.)

We expect the clinical features to have odds ratios greater than 1, which would suggest that heuristics are being followed. This holds for most of the significant effects with one exception: the promote heuristic for fatigue, which has an odds ratio of 0.77 (0.73–0.81), suggesting that this heuristic is not only not followed, but is inconsistent with common clinical practice. The other significant effects for clinical features have odds ratios ranging from 1.25 to 2.54. We find similar results in Site B,

Table 3
Odds ratios and 95% confidence intervals of logistic regression results.
Logistic regression results and rates of heuristic following rates for patients with and without each clinical feature for each heuristic. Terms with *p* values that are significant at a 0.05 level with a Bonferroni correction across all heuristics (15 terms for a threshold of 0.0033) are bolded. Odds ratios > 1.1 and <0.9 for significant terms are marked with an asterisk. For the Clinical Feature by Provider odds ratios, values larger than 1 indicate that psychiatrists are more likely to follow the heuristic.

Heuristic type	Clinical feature	Heuristic following rates w/out clinical feature	Heuristic following rates with clinical feature	Unadjusted clinical feature OR with 95% CI	Clinical feature OR with 95% CI	Clinical feature by provider odds ratio with 95% confidence intervals
Avoid	QT prolongation	0.57	0.6	1.13(0.86–1.48)	1.12(0.84–1.49)	0.77(0.3–1.98)
	Nonadherence	0.84	0.87	1.22(0.99–1.5)	1.12(0.89–1.4)	1.3(0.71–2.37)
	Sexual dysfunction	0.27	0.34	**1.43(1.24–1.64)***	**1.33(1.15–1.55)***	1.69(1.07–2.67)
	Overweight	0.94	0.97	**2.18(1.86–2.54)***	**2.2(1.86–2.6)***	1.12(0.7–1.78)
	Poor concentration	0.9	0.89	0.94(0.8–1.1)	0.8(0.67–0.95)	1.87(1.23–2.84)
	Suicidality	0.4	0.46	1.27(0.98–1.64)	1.31(0.96–1.78)	0.83(0.47–1.45)
	Underweight	0.42	0.52	**1.5(1.38–1.63)***	**1.42(1.3–1.55)***	1.12(0.86–1.47)
Promote	Anxiety	0.53	0.58	**1.23(1.18–1.29)***	**1.25(1.19–1.31)***	1.05(0.92–1.2)
	Nonadherence	0.14	0.13	0.87(0.71–1.08)	0.86(0.67–1.09)	1.21(0.73–2.03)
	Sexual dysfunction	0.25	0.29	1.19(1.03–1.38)	1.05(0.9–1.24)	1.65(1.04–2.6)
	Fatigue	0.44	0.38	**0.76(0.73–0.8)***	**0.77(0.73–0.81)***	1.04(0.89–1.22)
	Insomnia	0.54	0.56	**1.08(1.03–1.14)**	1.04(0.98–1.1)	1.0(0.86–1.17)
	Overweight	0.2	0.24	**1.28(1.21–1.37)***	**1.32(1.24–1.41)***	0.84(0.68–1.05)
	Poor concentration	0.2	0.24	**1.22(1.08–1.36)***	0.95(0.82–1.09)	**1.8(1.39–2.33)***
	Underweight	0.05	0.13	**2.94(2.59–3.34)***	**2.54(2.21–2.93)***	0.78(0.52–1.15)

Table 4
Odds ratios and 95% confidence intervals of logistic regression results - Cohort B.
Logistic regression results and rates of heuristic following rates for patients with and without each clinical feature for each heuristic in site B. Terms with p values that are significant at a 0.05 level with a Bonferroni correction across all heuristics (15 terms for a threshold of 0.0033) are bolded. Odds ratios > 1.1 and <0.9 for significant terms are marked with an asterisk. For the Clinical Feature by Provider odds ratios, values larger than 1 indicate that psychiatrists are more likely to follow the heuristic. Additionally, changes in significance or magnitude of odds a ratio from the Site A results are coded in red.

Heuristic type	Clinical Feature	Heuristic following rates w/out clinical feature	Heuristic following rates with clinical feature	Unadjusted clinical feature OR with 95% CI	Clinical feature OR with 95% CI	Clinical feature by provider odds ratio with 95% confidence intervals
Avoid	QT prolongation	0.58	0.68	1.58(1.12–2.25)	1.53(1.07–2.21)	0.93(0.23–3.8)
	Nonadherence	0.83	0.91	**2.05(1.41–2.99)***	1.8(1.2–2.71)	0.4(0.13–1.23)
	Sexual dysfunction	0.24	0.4	**2.11(1.68–2.64)***	**1.63(1.27–2.1)***	1.77(0.95–3.29)
	Overweight	0.95	0.97	**1.6(1.33–1.94)***	**1.57(1.28–1.94)***	1.62(0.96–2.76)
	Poor concentration	0.9	0.92	1.29(0.95–1.75)	1.08(0.77–1.51)	1.99(0.86–4.65)
	Suicidality	0.42	0.57	1.79(1.11–2.91)	1.82(1.08–3.08)	0.72(0.18–2.82)
	Underweight	0.42	0.58	**1.85(1.62–2.12)***	**1.78(1.54–2.05)***	0.94(0.61–1.47)
	Anxiety	0.55	0.59	**1.21(1.14–1.29)***	**1.27(1.19–1.37)***	**0.69(0.57–0.83)***
Promote	Nonadherence	0.14	0.16	1.09(0.81–1.47)	1.13(0.83–1.53)	0.18(0.02–1.38)
	Sexual dysfunction	0.21	0.32	**1.77(1.39–2.24)***	1.27(0.97–1.65)	1.4(0.75–2.61)
	Fatigue	0.41	0.34	**0.75(0.69–0.8)***	**0.76(0.7–0.83)***	1.18(0.92–1.51)
	Insomnia	0.55	0.58	**1.16(1.08–1.24)***	**1.12(1.04–1.21)***	1.06(0.84–1.32)
	Overweight	0.16	0.17	1.11(1.01–1.21)	**1.21(1.09–1.33)***	0.88(0.64–1.21)
	Poor concentration	0.16	0.24	**1.66(1.36–2.02)***	**1.43(1.13–1.79)***	1.47(0.93–2.33)
	Underweight	0.05	0.19	**4.58(3.84–5.47)***	**3.7(3.03–4.51)***	1.13(0.67–1.89)

where the fatigue-promote heuristic has odds ratio 0.76 (0.70–0.83).

We next investigated how heuristics are followed by psychiatrists compared to non-psychiatrist prescribers by examining the coefficient of the interaction term for the provider by the clinical feature in Table 3. We observed no significant effect for almost all heuristics with one exception: the 'promote' heuristic for poor concentration, which yields an odds ratio of 1.80 (1.39–2.33). In Site B, the provider by clinical feature interactions terms largely do not have significant effects, as in site A.

As a sensitivity analysis, we determined the robustness of these results to alternative codings of the clinical features in 2 ways: by varying the time window in which the feature must be observed and by varying the number of codes needed to count the feature as observed. Tables of odds ratios and 95% confidence intervals for the logistic regression analysis can be found in Supplemental Table 2 and Supplemental Table 3. Results were generally consistent, although some differences emerge (i.e., 1 difference each in 3 of the 4 analyses in the sexual dysfunction-avoid and poor concentration promote heuristics).

Finally, we sought to compare the magnitude of clinical feature effects to sociodemographic features, as a way of understanding effect size in more clinically-interpretable terms. See Supplemental Table 4 for the odds ratios and 95% confidence intervals for all variables we adjust for in the logistic regression analysis. We found comparably-sized effects for gender, ranging from 0.48 (0.44–0.52) in the underweight-promote rule, to 2.08 in the overweight-avoid rule, as to the clinical features, ranging from 0.77 (0.73–0.81) to 2.54 (2.21–2.93). We see similar ranges of effect sizes in insurance (range: 0.5 (0.45–0.55) to 1.93 (1.7–2.18)), as well as for other variables.

4. Discussion

In this analysis of longitudinal data from more than 45,000 antidepressant-treated individuals across psychiatry and non-psychiatry providers, we observed associations between clinical features and application of common prescribing heuristics, generally consistent across psychiatrists and non-psychiatrists, and across two sites. We emphasize that these heuristics are *not* trying to reflect FDA labels, which clinicians may not consistently consult, but simply a subset of heuristics commonly referenced in guidelines and teaching materials. Taken together, these results provide some support for the hypothesis that clinicians follow simple heuristics when prescribing antidepressants, while also indicating that demographic and provider variables have effect sizes comparable to the features themselves.

One exception to this finding is the reversed effect for the fatigue-promote rule that we find in both sites. The odds ratios of 0.69–0.8 for this clinical feature suggest that clinicians consistently reverse this heuristic instead of following it. The reason for this discordance merits further investigation; while the heuristics investigated here were curated by expert psychopharmacologists, this one may simply conflict with common practice.

While we find consistent, statistically significant effects of these prescribing heuristics on clinical practice, the effect sizes are generally modest, equivalent to those observed for sociodemographic features. We note several possible limitations that may explain this. First, some of the medications that are listed as those to avoid in Table 2 are already drugs that are prescribed less frequently (Table 3), possibly as a result of tolerability or safety concerns; as such, the magnitude of effect would be expected to be small.

Furthermore, and more importantly, we rely on coded clinical data, which is likely to substantially underestimate prevalence of particular clinical features, leading us to underestimate rates of adherence with heuristics. (That is, insomnia is certainly far more commonly observed in clinical practice than billing codes would suggest.) In this context, the fact that the absolute prescribing rates do show detectable effects of heuristics is particularly notable. For more commonly-applied codes, including over- and underweight diagnoses, larger effect sizes were observed. A useful extension in future work will be to examine the extent to which features documented in narrative clinical notes, rather than solely in diagnostic codes, may impact clinician prescribing.

Beyond the reliance on coded clinical data, we note several additional limitations. We cannot directly model the numerous other features that may impact prescribing choices, nor are we able to access provider-level features (e.g., years in practice, or exposure to continuing education) that may impact medication choice, because of constraints imposed by the institutional review board. Moreover, in many cases there are treatment options that are neither promoted nor avoided under our heuristics, which would tend to dilute our ability to detect effects of these principles.

5. Conclusions

Taken together, our results support the often-asserted hypothesis that clinicians do follow heuristics in treatment selection, at least in a subset of patients. As efforts to implement precision medicine in psychiatry accelerate, these results provide a baseline understanding of how clinicians currently make treatment decisions. This work further suggests that, by providing additional heuristics, it may be possible to influence prescribing in order to improve antidepressant treatment outcomes.

Data sharing statement

The data used for this project are composed of confidential health information used under specific approval from the Partners HealthCare Institutional Review Board. These data cannot be released or used beyond the scope of approved protocols covering enumerated investigators because of the risk of re-identification.

Code availability statement

Code will be released on github and at the authors' web site.

CRediT authorship contribution statement

All authors contributed to drafting and revising the manuscript. IL and MFP contributed to analyzing data. RHP and FDV contributed to overseeing the project.

Declaration of competing interest

The authors report no conflicts of interest. They report the following financial disclosures. RHP holds equity in Psy Therapeutics and Outermost Therapeutics; serves on the scientific advisory boards of Genomind and Takeda; and consults to RID Ventures. RHP receives research funding from NIMH, NHLBI, NHGRI, and Telefonica Alfa. RHP is an associate editor for JAMA Network Open. THM receives research funding from the Stanley Center at the Broad Institute, the Brain and Behavior Research Foundation, National Institute of Aging, and Telefonica Alfa. FDV consults for Davita Kidney Care and Google Health. The other authors have no disclosures to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.04.128.

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