

## NEUROIMAGING

# Amyloid duration is associated with preclinical cognitive decline and tau PET

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### Abstract

**Introduction:** This study applies a novel algorithm to longitudinal amyloid positron emission tomography (PET) imaging to identify age-heterogeneous amyloid trajectory groups, estimate the age and duration (chronicity) of amyloid positivity, and investigate chronicity in relation to cognitive decline and tau burden.

**Methods:** Cognitively unimpaired participants ( $n = 257$ ) underwent one to four amyloid PET scans (Pittsburgh Compound B, PiB). Group-based trajectory modeling was applied to participants with longitudinal scans ( $n = 171$ ) to identify and model amyloid trajectory groups, which were combined with Bayes theorem to estimate age and chronicity of amyloid positivity. Relationships between chronicity, cognition, clinical progression, and tau PET (MK-6240) were investigated using regression models.

**Results:** Chronicity explained more heterogeneity in amyloid burden than age and binary amyloid status. Chronicity was associated with faster cognitive decline, increased risk of abnormal cognition, and higher entorhinal tau.

**Discussion:** Amyloid chronicity provides unique information about cognitive decline and neurofibrillary tangle development and may be useful to investigate preclinical Alzheimer's disease.

### KEYWORDS

Alzheimer's disease, Alzheimer's, beta-amyloid, biomarker, chronicity, group-based trajectory modeling, positron emission tomography, tau, trajectory modeling

## 1 | INTRODUCTION

Alzheimer's disease (AD) is characterized by amyloid  $\beta$  ( $A\beta$ ) plaques and neurofibrillary tau tangles that accrue over time, leading to

neurodegeneration and progressive cognitive and functional decline. Positron emission tomography (PET) biomarkers enable in vivo detection of pathophysiologic  $A\beta$  and tau, and as hypothesized by Jack and colleagues,<sup>1,2</sup> these AD biomarkers follow nonlinear

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longitudinal patterns where detectable pathologic  $A\beta$  accrues first,<sup>3,4</sup> perhaps 20 or more years before clinically detectable cognitive impairment.<sup>5,6</sup> The 2018 Research Framework for AD<sup>7</sup> proposes that amyloid PET may be used to ascertain amyloid status (ie, amyloid positive or negative [A+/-]). This dichotomization is heuristically useful, and multiple studies have shown that A+ cognitively unimpaired individuals exhibit greater cognitive decline over time than individuals who are A-,<sup>8-10</sup> with greater cognitive decline for people who exhibit both elevated pathologic amyloid and tau.<sup>11,12</sup> However, among individuals who are accumulating amyloid, there is considerable heterogeneity in the magnitude and onset of amyloid accumulation with respect to age.<sup>6,13,14</sup> A method for elucidating such heterogeneity in amyloid-accumulating cases may improve prediction models of the temporal biomarker cascade and cognitive decline.

As observed by Jack et al. in their seminal paper,<sup>1</sup> there is little known about inter-individual differences in middle-age  $A\beta$  accumulation when individuals are transitioning from undetectable (A-) to detectable (A+) amounts of  $A\beta$ . The theoretical sigmoidal model of  $A\beta$  accumulation<sup>1</sup> suggests that individuals have relatively slow accumulation initially, followed by faster accumulation as the disease progresses. Several approaches have examined ways to empirically assess the trajectory of  $A\beta$  biomarkers in AD.<sup>6,13,15,16</sup> These approaches often attempt to align persons within a disease state to mitigate the biomarker heterogeneity with respect to age. A method that combines  $A\beta$  magnitude and amyloid measurement age to estimate the age at biomarker onset (ie, A+) could be useful in such scenarios because it would allow realignment of the time axis to describe the duration, or chronicity, of A+ relative to that person's age at any given procedure. Group-based trajectory modeling (GBTM) is used to describe the developmental course(s) a phenomenon might follow over time,<sup>17,18</sup> and it is well-suited for characterizing potential sub-distributions of PET measured  $A\beta$  pathology accumulation patterns with respect to age. Modeling these sub-distributions in a sample containing amyloid converters across the age spectrum may allow for more accurate estimation of the age at which persons become A+.

Using data from the Wisconsin Registry for Alzheimer's Prevention (WRAP) study we investigated the following aims. First, we used longitudinal Pittsburgh compound B (PiB) to identify and characterize  $A\beta$  trajectory groups of non-demented healthy middle-aged participants. Second, we examined whether trajectory group membership could be reliably obtained from only one PiB scan. We next utilized this trajectory group information to estimate the age at A+ (ie, PiB positivity, [PiB(+)]) onset, and thereby, the chronicity of A+ (ie, time between estimated A+ onset and age at a given assessment). Third, we characterized mathematically the shape of the amyloid accumulation curve observed in this sample. Fourth, we investigated whether A+ chronicity was associated with cognitive decline and with tau tangles. Tau tangles were assessed using [<sup>18</sup>F]MK-6240, a novel PET radioligand with a high affinity for neurofibrillary tangles and minimal off-target binding in the brain.<sup>19,20</sup>

## HIGHLIGHTS

- Group-based trajectory modeling identifies age-based amyloid trajectory groups.
- Longitudinal trained algorithm can estimate age and duration of amyloid positivity.
- Amyloid-positive duration accounts for age-based amyloid accumulation heterogeneity.
- Longer amyloid duration is associated with greater tau burden and cognitive decline.
- Individuals with younger age at amyloid onset are more likely to be apolipoprotein  $\epsilon 4$  carriers.

## RESEARCH IN CONTEXT

Previous studies have indicated that Alzheimer's disease (AD) has an extended prodromal period of two or more decades wherein pathological amyloid  $\beta$  ( $A\beta$ ) and tau proteins are aggregating prior to overt symptomology. Understanding longitudinal accumulation trajectories of amyloid and tau biomarkers is an area of active research, which is confounded by heterogeneity in these trajectories with respect to age. This study demonstrates a novel approach to estimating the age at amyloid onset informed by longitudinal positron emission tomography (PET) imaging. The results indicate that this approach can estimate the age at amyloid positivity within individuals, and thereby, the chronicity of amyloidosis, operationalized as duration of amyloid exposure at a given procedure. Application of this method has suggested that amyloid chronicity explains considerable heterogeneity in age-related amyloid accumulation trajectories and is associated with longitudinal cognitive decline and PET measured entorhinal tau tangles. This approach may enable an intuitive way to investigate temporal sequences in AD.

## 2 | METHODS

### 2.1 | Sample

The sample included 257 WRAP participants who were cognitively unimpaired at baseline and completed at least one PiB PET scan as of June 2019 (Table 1). WRAP is a longitudinal observational cohort study of late middle-aged and older adults, enriched for risk of AD by oversampling participants with a parental history of AD (73% parental AD history; see Johnson et al.<sup>21</sup>). All study procedures were approved by the University of Wisconsin-Madison Institutional Review Board and are in concordance with the Helsinki declaration.

**TABLE 1** Sample characteristics: overall and by PiB trajectory group

	Overall N	Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	Group 4 n(%)	P- value <sup>a</sup>	Differing pairs
	257	178(69.3)	39(15.2)	21(8.2)	19(7.4)		
PACC-3 baseline age, mean(SD) <sup>b</sup>	59.1(6.2)	58.3(6.6)	61.3(5.3)	60.8(4.6)	59.1(4.5)	0.025	1 versus 2
PACC-3 follow-up years, mean(SD) <sup>b</sup>	7.2(2.3)	7.2(2.1)	6.4(2.8)	8.0(2.0)	7.4(2.5)	0.064	
PACC-3 baseline performance, mean(SD) <sup>b</sup>	0.055(0.75)	0.08(0.75)	-0.10(0.79)	0.04(0.73)	0.13(0.66)	0.55	
WRAT3 reading, mean(SD)	107.0(9.1)	106.8(9.5)	107.6(8.1)	105.5(9.2)	108.6(7.5)	0.71	
Years of education, median [Q1-Q3]	16 [14-18]	16 [14-18]	17 [14-18]	17 [16-17]	17 [14-18]	0.68	
Female, n(%)	175(68.1)	125(70.2)	22(56.4)	13(61.9)	15(79.0)	0.25	
Parental history of AD, n(%)	181(70.7)	118(66.7)	30(76.9)	15(71.4)	18(94.7)	0.044	1 versus 4
APOE ε4 carrier, n(%)	103(40.2)	55(31.2)	19(48.7)	16(76.2)	13(68.4)	<0.0001	1 versus 2-4
Non-Hispanic Caucasian, n(%)	241(93.8)	167(93.8)	36(92.3)	21(100.0)	17(89.5)	0.52	
PiB age first scan, mean(SD)	62.1(6.6)	61.4(6.9)	64.2(6.2)	64.1(4.7)	62.7(5.5)	0.050	1 versus 2
PiB age at most recent scan, mean(SD)	66.4(6.7)	65.6(7.1)	68.3(5.9)	69.1(4.9)	66.9(4.8)	0.028	1 versus 2-3
PiB chronicity at most recent scan, mean(SD)	-12.9(13.1)	-20.2(4.8)	-4.4(7.6)	7.2(5.4)	15.9(5.0)	<0.0001	All pairs
PiB(+) <sup>c</sup> , n(%)	55(21.4)	1(0.6)	16(41.0)	20(95.2)	19(100.0)	<0.0001	1 versus 2-4; 2 versus 3-4
MK-6240 PET subset (n = 198)	198	136(68.7)	30(15.2)	16(8.1)	16(8.1)		
Age at MK-6240 scan, mean(SD) years	67.6(6.4)	66.7(6.8)	70.0(4.7)	70.1(4.8)	67.4(5.1)	0.025	1 versus 2-3
Time between PiB and MK, mean(SD) years	0.099(0.32)	0.089(0.32)	0.17(0.38)	0.089(0.34)	0.055(0.15)	0.58	
PiB Chronicity at MK-6240 scan, mean(SD)	-11.8(13.3)	-19.6(4.5)	-2.5(6.4)	8.3(5.1)	16.5(5.3)	<0.0001	All pairs
Entorhinal cortex SUVR, median [Q1-Q3]	1.01 [0.92-1.12]	0.99 [0.91-1.09]	1.02 [0.92-1.12]	1.21 [0.96-1.51]	1.47 [1.00-2.02]	0.0004	1-2 versus 3-4

Abbreviations: APOE, apolipoprotein E; PACC-3, Preclinical Alzheimer Cognitive Composite (3 tests); PET, positron emission tomography; PiB, Pittsburgh compound B; Q1-Q3, first to third quantile; SD, standard deviation; SUVR, Standard uptake value ratio; WRAT3, Wide Range Achievement Test (3rd edition).

<sup>a</sup>Statistical tests: chi-square or Fisher's exact for categorical; analysis of variance (ANOVA) for continuous where mean(SD) reported; Kruskal-Wallis for continuous where median [Q1-Q3] reported. Post hoc pairwise group differences at unadjusted  $P < 0.05$  noted in right-hand column. For example, 1 versus 2, 3 indicates group 1 differed from group 2 and group 3 in separate pairwise comparisons.

<sup>b</sup>PACC-3  $n = 254$

<sup>c</sup>PiB(+) defined as any global PiB DVR within a person  $\geq 1.2$ . The group 1 PiB(+) participant was PiB negative as of their most recent scan with global PiB DVRs of 1.20, 1.17, and 1.13 at ages 66, 68, and 72, respectively.

## 2.2 | Cognitive assessment

WRAP participants completed cognitive assessments at baseline, and approximately every 2 years thereafter. Longitudinal cognitive performance was assessed using a three-test Preclinical Alzheimer's Cognitive Composite (PACC-3) score,<sup>10,22</sup> derived from the Rey Auditory Verbal Learning Test (RAVLT; Trials 1-5),<sup>23</sup> Logical Memory II,<sup>24</sup> and digit symbol substitution.<sup>25</sup>

## 2.3 | Neuroimaging

All participants underwent T1-weighted magnetic resonance imaging (MRI), and [<sup>11</sup>C]PiB ([<sup>11</sup>C]6-OH-BTA-1).<sup>26</sup> Amyloid burden was assessed as a global cortical average PiB distribution volume ratio (DVR)<sup>27</sup> and a threshold of  $DVR \geq 1.2$ <sup>28</sup> to ascertain PiB(+); 198 also underwent [F-18]MK-6240 (6-(Fluoro-<sup>18</sup>F)-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine) PET imaging.<sup>19</sup> Radioligand

synthesis and PET and MRI acquisition, processing, and analysis methods have been described previously<sup>20,29</sup> and in *supplemental materials*.

## 2.4 | Statistical methods

Statistical analyses were conducted in SAS and R. Sample characteristics were compared across groups of interest (eg, PiB trajectory groups) using tests appropriate for the distribution of the data. Tests included chi-square, fisher's exact, analysis of variance (ANOVA) and Kruskal-Wallis.

### 2.4.1 | Aim 1

We used GBTM on the 171 participants with two to four PiB scans to identify PiB trajectory groups. GBTM is a special case of pattern mixture modeling in which individuals are classified into groups on the basis of longitudinal data.<sup>17,30,31</sup> Models are fit iteratively by adding and removing groups based on the Bayesian information criteria (BIC) fit statistics.<sup>17,30</sup> We modeled trajectories using up to a cubic polynomial, selecting the best parameterization based on BIC fit and reasonableness of the results. For example, if two functions had similar BIC for a group, the model that was more biologically probable was selected (ie, accumulating groups were not allowed to estimate PiB DVR values less than that of the non-accumulating group).

### 2.4.2 | Aim 2

Using the GBTM functions and Bayes theorem (Equation 1, Table 2) to estimate the probability of group membership in group "j" for each participant's most recent scan, two re-weightings of the Bayes probabilities were applied to up-weight the probability of group 1 or 2 for low global PiB DVR values in age ranges where the trajectory functions were parallel and close (additional details described in supplement). Trajectory group membership was assigned as the group with maximum probability. Agreement between GBTM and Bayes theorem-derived trajectory group assignments was examined using Kappa statistics.<sup>32</sup>

### 2.4.3 | Aim 3

After observing strong agreement between PiB trajectory group assignment methods, the Bayes theorem approach was applied to all 257 participants to ascertain the probability of group membership and group assignment based on their global PiB DVR at their most recent scan. A+ age was then estimated for each participant using a probability weighted average of the A+ ages of the trajectory groups (Table 2, Equation 2). Amyloid chronicity was then calculated for each PET scan as the age at scan minus the estimated A+ age (Table 2, Equation 3). By this convention, positive chronicity indicates the estimated duration of

**TABLE 2** Equations

Equation no.	Equation
1	$\Pr(\text{Membership in Group J}) = \Pr(\text{Group J} \text{Observed PiB}) = \Pr(\text{Group J}) \cdot \Pr(\text{Observed PiB} \text{Group J}) / \Pr(\text{Observed PiB})$
2	$\text{Age PiB}(+) \approx \Pr(\text{Membership in group 1}) \cdot \text{group 1 Age} + \Pr(\text{Membership in group 2}) \cdot 71.3 + \Pr(\text{Membership in group 3}) \cdot 61.6 + \Pr(\text{Membership in group 4}) \cdot 50.6$
3	$\text{PiB chronicity (at time of PiB scan)} \approx \text{Age at PiB scan} - \text{age PiB}(+)$
4	$\text{Group 1 global PiB DVR ("PiB")} \approx 1.0571$
5	$\text{Group 2 PiB} \approx 1.1219 + 0.00941 \cdot \text{c65\_age} + 0.00049 \cdot \text{c65\_age}^2$
6	$\text{Group 3 PiB} \approx 1.2835 + 0.02572 \cdot \text{c65\_age} + 0.00012 \cdot \text{c65\_age}^2 + -0.00005 \cdot \text{c65\_age}^3$
7	$\text{Group 4 PiB} \approx 1.6370 + 0.03789 \cdot \text{c65\_age} + 0.00052 \cdot \text{c65\_age}^2$
8	$\text{Global PiB DVR} \approx 1.233 + 0.0186 \cdot \text{PiB Chronicity} + 0.000444 \cdot \text{PiB Chronicity}^2$
9	$\text{Global PiB DVR} \approx 1.225 + 0.0166 \cdot \text{PiB Chronicity} + 0.000612 \cdot \text{PiB Chronicity}^2$

Abbreviations: DVR, distribution volume ratio; GBTM, group-based trajectory modeling; PiB, Pittsburgh compound B.

Equation 1 notes:  $\Pr(\text{Group J})$  = proportion assigned to each group via GBTM (for  $j$  = groups 1–4, respectively).  $\Pr(\text{Observed PiB}|\text{Group J})$  was obtained by getting the mean(SD) residual for all scans of people assigned to group J and using these values to convert residuals for group J to z-scores. We then used the normal distribution to obtain the probability of observing a residual as or more extreme than that one relative to Group J. Similarly,  $\Pr(\text{Observed PiB})$  was calculated as the probability of observing a global PiB DVR as or more extreme than the observed PiB. Post-Bayes theorem re-weightings for two conditions are described in supplemental materials. Equation 2 note: "Group 1 Age" is the estimated life expectancy given participant's sex and current age.

Equation 3 note: In general, PiB chronicity at any assessment of interest = age at the assessment of interest minus estimated age PiB(+).

Equations 4–7 note: "c65\_age" indicates age centered at age 65.

PiB(+), whereas negative chronicity indicates the person was PiB(–) at the time of the scan. Global PiB DVR was then modeled as a function of amyloid chronicity (including linear and quadratic chronicity terms). This function was used to estimate the time duration from the 10th and 90th PiB DVR centiles of the accumulating groups to the PiB(+) threshold to enable comparisons of amyloidosis duration with this method and sample to other studies.

### 2.4.4 | Aim 4

We used linear mixed-effects (LME) models to examine whether amyloid chronicity at baseline PACC-3 modified longitudinal PACC-3 scores (random intercept and age-related slope; unstructured covariance;  $n = 254$  after excluding one participant with multiple sclerosis and two missing PACC-3 scores). Fits of the base model (covariates of sex, Wide Range Achievement Test 3 [WRAT3], practice, age, and age<sup>2</sup>) were compared with a model that

included amyloid chronicity and its interaction with age and age<sup>2</sup>. After observing better model fit (a sufficiently lower value of the corrected-Akaike information criteria [AICc] statistics<sup>33</sup>) for the latter model and significant interactions, we depicted the effects of amyloid chronicity on cognitive trajectories by plotting age trajectories for amyloid chronicity values that represented mean chronicity at PACC-3 baseline in each of the four PiB trajectory groups.

In secondary analyses, we used logistic regression to examine whether concurrent amyloid chronicity and age were associated with increased risk of abnormal cognition at the most recent visit using three definitions of abnormal (progression to clinical impairment, abnormal relative to internal cross-sectional norms, and abnormal relative to longitudinal norms; see *supplemental materials*).

We used regression to compare age and amyloid chronicity at MK-6240 scan, PiB(+/-) status, and PiB DVR as predictors of entorhinal cortex MK-6240 standard uptake value ratio (SUVR). In separate models for each continuous predictor (age and amyloid chronicity), we began with cubic polynomial terms with the plan of sequentially removing non-significant highest order terms. To estimate how the PiB trajectory groups differed in terms of increase in MK-6240 per year of amyloid chronicity, we also used output from a model including a PiB trajectory group\*chronicity interaction.

Sensitivity analyses were performed for all outcomes, substituting PiB(+/-) status and PiB DVR for amyloid chronicity and comparing AICc model fit statistics across otherwise identical models and consider  $|\Delta\text{AICc}|$  values  $<2$  to represent comparable models.<sup>33</sup>

## 3 | RESULTS

### 3.1 | Aim 1

In the subset used for GBTM ( $n = 171$ ), mean(SD) age at first scan was 61.1(6.1) [range 46.9–78.9] with mean(SD) = 5.8(2.0) years between first and last scan. Thirty-seven (21.6%) were PiB(+) for at least one scan, 114 (66.7%) were female, 162 (94.7%) were non-Hispanic Caucasian, 70(40.9%), apolipoprotein E  $\epsilon 4$  carriers (APOE4), and 124 (72.5%) had a parental history of AD dementia.

GBTM identified four age-defined PiB trajectory groups. Mean and median probabilities of group membership exceeded 70% in each group (indicating support for the four group solution). GBTM assigned 125 (73.1%) to a non-accumulating group (group 1), 21 (12.3%) to a latest accumulating group (group 2), 14 (8.2%) to the middle accumulating group (group 3), and 11 (6.4%) to the earliest accumulating group (functions defining groups 1–4 are equations 4–7, respectively, in Table 2). Group functions and observed data are shown in Figure 1A.

Solving equations 5 through 7 yielded estimated ages of PiB(+) of 71.3, 61.6, and 50.6 years for groups 2 through 4, respectively. Group 1 indicated an intercept only model that was below the PiB(+) threshold. Therefore, we estimated age at PiB(+) as age at PET scan plus life expectancy from a gender-specific life expectancy table (<https://www.dhs.wisconsin.gov/stats/life-expectancy.htm>; accessed 7/23/2019); this resulted in mean(SD) estimated age PiB(+) for group 1 = 88.0(2.2).

### 3.2 | Aim 2

We observed strong agreement between PiB trajectory group assignment using GBTM (longitudinal scans) versus using trajectory group functions and Bayes theorem (only most recent scan in the GBTM set). Specifically, 160 of 171 group assignments agreed (93.6% agreement; simple Kappa statistic = 0.86, 95% confidence interval [CI] 0.78–0.94) with perfect agreement in groups 3 and 4. GBTM and Bayes theorem-derived group membership probabilities were highly correlated (Spearman 0.87 for 160 concordant cases, 0.85 including 11 discrepancies; see supplement for details of discrepant cases). For all subsequent analyses, group membership based on Bayes theorem and most recent PiB scan is used.

### 3.3 | Aim 3

Using the Bayes theorem approach, we obtained group membership probabilities for all 257 participants, including 86 not included in GBTM modeling, which was used to assign PiB trajectory group membership (sample characteristics in Table 1). Equations 2 and 3 (Table 2) were then used to estimate amyloid chronicity for all participants based on their last PiB scan.

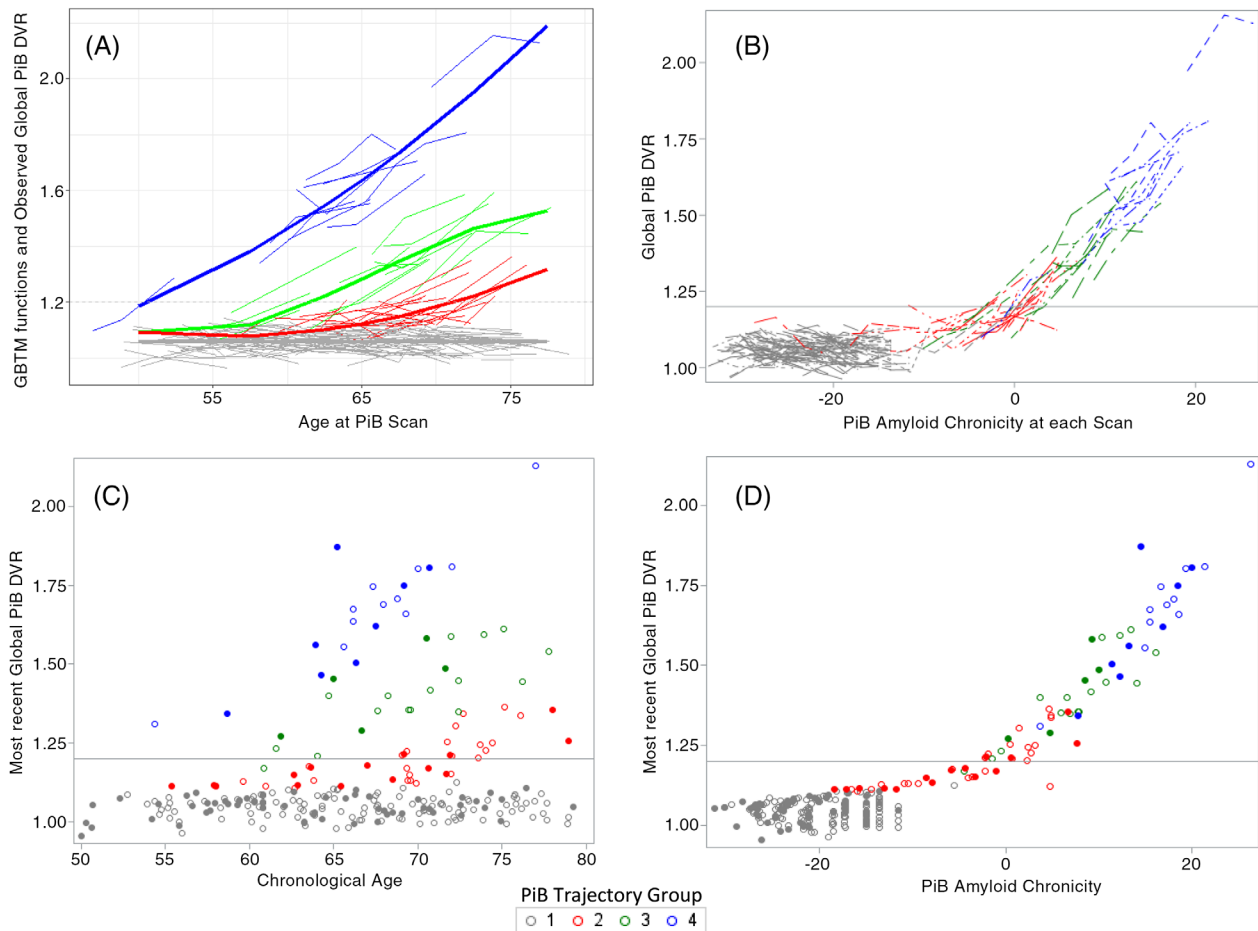
The four trajectory groups did not differ in terms of baseline PACC-3 performance, WRAT3 reading, years of education, race, or sex, but did differ in amyloid chronicity at most recent scan, parental history of AD, and APOE4 carriage. Follow-up pairwise comparisons among trajectory groups showed more APOE4 carriage in each of the accumulating groups compared to group 1 and more parental history of AD in group 4 (the earliest accumulating group) compared to group 1.

Plots depicting PiB DVR versus chronicity and chronological age are shown in Figure 1 (1B shows longitudinal plots for the GBTM subset; Figure 1C and D are plotted cross-sectionally using most recent PiB). Chronicity and most recent PiB DVR were highly correlated (Pearson  $r = 0.895$ ), with a quadratic model indicating a good fit for chronicity predicting PiB DVR ( $R^2 = 0.945$  for all 257 participants,  $R^2 = 0.931$  including only groups 2–4; Table 2 Equations 8 and 9, respectively). Using Equation 9, we estimated it would take 10.0 years to go from PiB DVR = 1.12 (10th centile of accumulating groups) to PiB(+), and another 17.7 years to reach PiB DVR = 1.71 (90th centile of accumulating groups).

### 3.4 | Aim 4

#### 3.4.1 | Cognition

LME models of longitudinal PACC-3 showed better fit after adding the amyloid chronicity terms to the model, including covariates and age terms ( $\Delta\text{AICc}$  decrease =  $-25.2$ ). Interaction effects are depicted in Figure 2 for values representing mean amyloid chronicity at baseline PACC-3 in each of the PiB trajectory groups. In sensitivity analyses, substituting PiB(+/-) status for amyloid chronicity also resulted in



**FIGURE 1** For all panels, gray indicates group 1 (non-accumulators), red = group 2, green = group 3, and blue = group 4. Horizontal line indicates PiB(+) threshold (global PiB DVR = 1.2). (A) Spaghetti plot of individual trajectories in set of 171 used in GBTM (thin lines) with four group functions identified by GBTM superimposed on the figure (thick lines; Equations 4–7 in Table 2). (B) Spaghetti plot of individual trajectories in set of 171 realigned versus amyloid chronicity. (C) Scatter plot of most recent Global PiB DVR versus chronological age in expanded set (171 original = circles, 86 new people = dots; colors indicate trajectory group). (D) Scatter plot of most recent Global PiB DVR versus amyloid chronicity in expanded set (coding same as above). Abbreviations: DVR, distribution volume ratio; GBTM, group-based trajectory modeling; PiB, Pittsburgh compound B

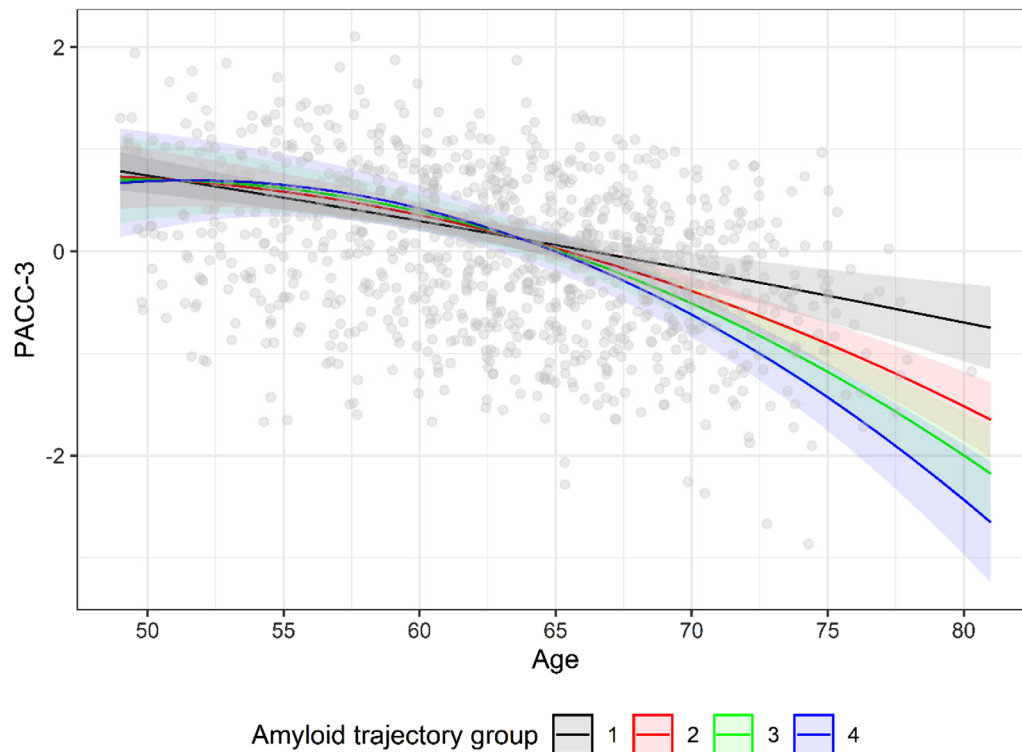
better fit ( $\Delta\text{AICc} = -12.8$ ) relative to the base model, but not as good a fit as using chronicity ( $\Delta\text{AICc} = -12.5$  model with amyloid chronicity AICc minus the model with PiB(+)) AICc).

Logistic regression showed a consistent pattern of statistically significant risk of abnormal cognitive status associated with amyloid chronicity but not age, where abnormal cognitive status was defined relative to clinical criteria and internal norms.<sup>34</sup> Odds ratios and CIs for age and amyloid chronicity are shown in Figure 3 for each of these outcomes. Compared to those who did not progress to mild cognitive impairment (MCI) or AD ( $n = 238$ ), those who progressed ( $n = 16$ ) were on average 4.8(6.2) years older at their most recent cognitive assessment, but were estimated to be amyloid positive for 15.5(12.5) years longer. Similarly, age and amyloid chronicity were 0.93(6.2) and 11.2(12.6) years higher in those below ( $n = 27$ ) versus above ( $n = 218$ ) the cross-sectional internal norms cutoff; and age and PiB chronicity were 2.8(6.2) and 11.2(12.6) years higher in those below ( $n = 28$ ) versus above ( $n = 217$ ) the longitudinal internal norm cutoff. Sensitivity

analyses substituting PiB(+/-) status for chronicity indicated worse fit statistics for all cognitive outcomes ( $\Delta\text{AICc}$  range =  $-6.2$  to  $-8.4$ ) compared to chronicity. Substituting last PiB DVR for chronicity indicated chronicity was a better fit for predicting MCI/AD and abnormal cross-sectional norms ( $\Delta\text{AICc}$ 's =  $-3.1$  and  $-3.3$ , respectively) but not for abnormal longitudinal norms ( $\Delta\text{AICc} = 2.8$ ).

### 3.4.2 | Entorhinal tau

One hundred ninety-eight participants (77%) also underwent MK-6240 PET scans (mean(SD) of 0.10(0.32) years between last PiB and MK-6240 scans; mean(SD) age at MK-6240 scan = 67.6(6.4)). Amyloid chronicity at the time of MK-6240 differed between all PiB trajectory groups in a stepwise manner (Table 1). Mean entorhinal MK-6240 SUVR was near 1 for groups 1 and 2, increased stepwise for groups 3 and 4, and indicated significant group differences ( $P = 0.0004$ ; groups 1



**FIGURE 2** Interaction plot from LME of PACC-3. Lines depict age trajectories for PiB chronicities of  $-28$ ,  $-11$ ,  $-1$ , and  $8$  (these values are the mean PiB chronicity at baseline PACC-3 of groups 1–4, respectively). Dots indicate observed PACC-3 values. Predicted  $\text{PACC-3} \approx -0.3658 + -0.4304 \cdot \text{Male} + 0.0291 \cdot \text{c100\_WRAT3} + 0.1142 \cdot \text{Practice} + -0.09149 \cdot \text{c65\_age} + -0.00182 \cdot \text{PiB chronicity} + -0.00305 \cdot \text{c65\_age}^2 + -0.00156 \cdot \text{c65\_age} \cdot \text{PiB chronicity} + -0.00010 \cdot \text{age}^2 \cdot \text{PiB chronicity}$  (and random person-level intercepts and age slopes);  $\text{c100\_WRAT3}$  indicates WRAT3 reading standard score, centered at value of 100 and  $\text{c65\_age}$  indicates age centered at 65. Abbreviations: LME, linear mixed effects model; PACC-3, preclinical alzheimer cognitive composite (3 tests); WRAT3, wide range achievement test (3rd edition)

and 2 differed from groups 3 and 4). Only the linear age term was a significant predictor of entorhinal cortex MK-6240 SUVR; in a separate model, all terms in the cubic amyloid chronicity polynomial model were significant predictors of entorhinal cortex MK-6240 SUVR (Figure 4;  $\Delta\text{AICc chronicity-age models} = -120.7$ ). Including the trajectory group term and its interaction with chronicity in the model indicated that MK-6240 SUVR values were 1.1, 3, and 10.6 times higher for the amyloid-accumulating groups (ie, groups 2–4, respectively) compared to the non-accumulating group (ie, group 1; interaction  $P$ -value  $< 0.0001$ ;  $\Delta\text{AICc chronicity polynomial-group} \cdot \text{chronicity interaction model} = -6.5$ ).

Sensitivity analyses replacing chronicity with PiB(+/-) status indicated that PiB(+/-) status was also a significant predictor of MK-6240 entorhinal cortex SUVR, although it was a weaker predictor than chronicity (Figure 4;  $\Delta\text{AICc chronicity-PiB(+)} \text{ models} = -81.5$ ). Replacing amyloid chronicity with Global PiB DVR yielded models with a similar fit ( $\Delta\text{AICc chronicity-global PiB DVR models} = -1.3$ ).

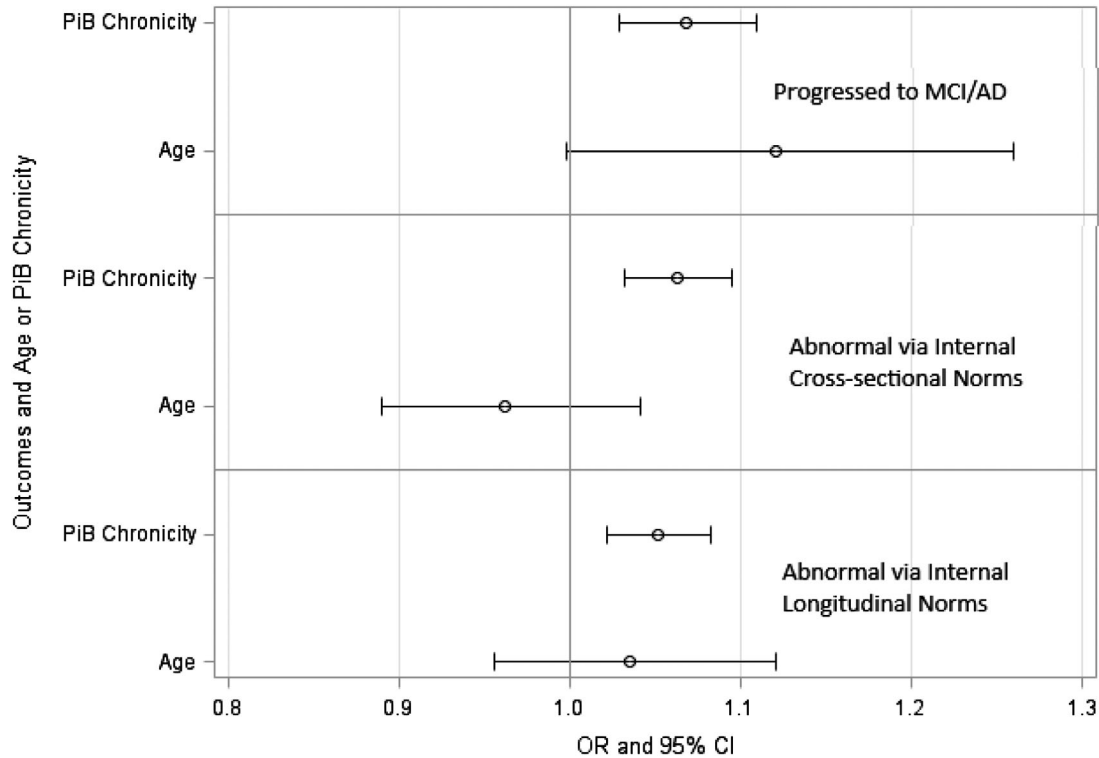
## 4 | DISCUSSION

This work demonstrates a novel application of GBTM and Bayes theorem to identify amyloid trajectory groups with respect to chronological age and to estimate the age of amyloid positivity within groups and

individuals, and thereby, the time duration of exposure to pathologic  $A\beta$  (ie, amyloid chronicity). This methodology was applied to investigate differences between trajectory groups and relationships between amyloid duration, chronological age, PET measured neurofibrillary tangles, and cognitive trajectories of initially cognitively unimpaired persons. Among the key findings was that the estimated duration of amyloid positivity (ie, amyloid chronicity) maintained information about dichotomous amyloid status while simultaneously preserving information about the severity of amyloidosis. In addition, this approach provided insights regarding the heterogeneity of amyloid accumulation trajectories with respect to age that become homogeneous when reordering the time-axis to reflect the estimated duration of amyloidosis.

### 4.1 | $A\beta$ modeling and rates of accumulation

Previous studies have used several different approaches and cohorts to model amyloid trajectories with respect to age and amyloid biomarker levels.<sup>1,6,15,35,36</sup> These studies suggest that individuals in the AD continuum begin accumulating  $A\beta$  at different ages, but experience similar rates of amyloid accumulation for a given level of amyloidosis. In agreement with these studies, the GBTM results suggest that there exist subgroups of amyloid accumulators that



**FIGURE 3** Forest plots of odds ratios (ORs) with various outcomes indicating abnormal at last cognitive assessment. The top pair of variables indicates ORs and their 95% confidence intervals (CIs) for predicting progression from Cognitively Unimpaired to mild cognitive impairment (MCI) or Dementia (cognitive statuses determined by consensus conference as described in Ref. 21). The middle pair of variables show ORs and CIs for predicting an abnormal PACC-3 score at the most recent cognitive assessment according to internal demographically adjusted cross-sectional norms (ie,  $\leq 7$ th centile or  $\sim 1.5$  SD or more below expected). The bottom pair of variables show ORs and CIs for predicting an abnormal change in PACC-3 score at the most recent cognitive assessment according internal longitudinal norms (ie,  $\leq 7$ th longitudinal centile). Additional abbreviations: PACC-3, preclinical alzheimer cognitive composite (3 tests); SD, standard deviation

differ in the age of PET-detectable amyloidosis onset, but the rates of amyloid accumulation with respect to time of amyloid onset are similar across individuals. This was demonstrated in this study by plotting the longitudinal amyloid data along the time axis realigned for duration of amyloid positivity and observing the similarity in slopes across subjects with similar durations of estimated amyloid positivity. In addition, the shape of these data were consistent with the early portion of the  $A\beta$  biomarker model of Jack et al.<sup>1</sup> However, we did not observe evidence of a slowing of the accumulation rate, which was potentially due to the sample being younger and primarily asymptomatic, and therefore, earlier in the AD continuum compared to other studies. Further work adding new longitudinal cases will be needed to examine to what extent the homogeneity in this curve is maintained in the presence of new longitudinal scans not used to fit the initial trajectory functions.

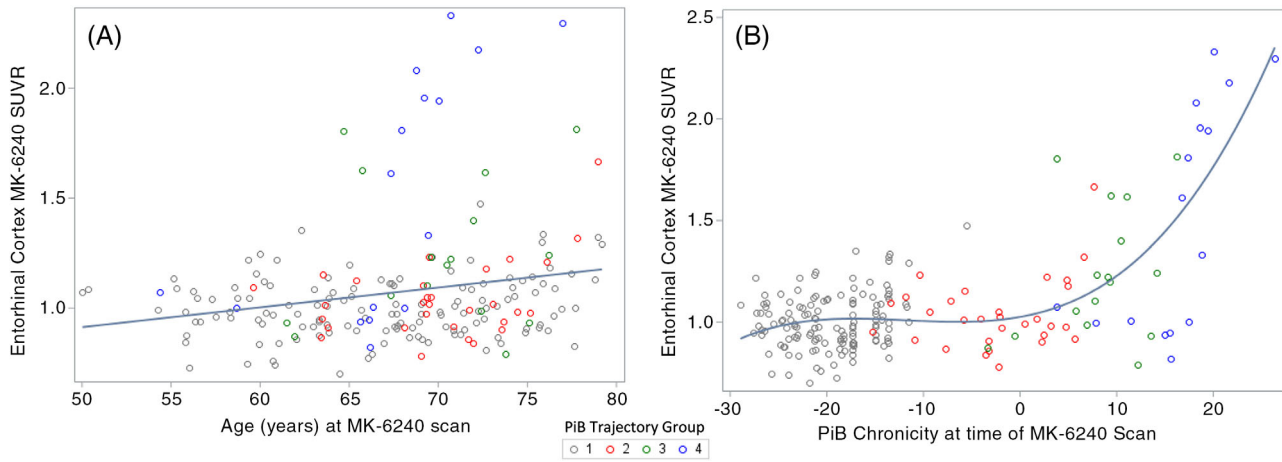
#### 4.2 | Chronology of $A\beta$ relative to tau and cognitive decline

Understanding the chronology of AD biomarkers and their prognostic value is important for contextualizing studies relating AD biomarkers to symptomatology and other disease outcomes, and for clinical trial

design. Previous studies have proposed different methods for obtaining metrics reflective of disease state.<sup>1,3,15,35-37</sup> In contrast to those methods, the approach in this study uses fewer model parameters and less complex model functions. Furthermore, the relative timing between chronological events is not affected by the positivity threshold, the output (time duration) is easily interpretable, and estimates can be obtained from a single cross-sectional PET scan once the group model is trained. A criticism of this approach is that amyloid chronicity is highly correlated with DVR estimates ( $r = 0.90$ ). However, by recasting the magnitude of amyloid elevation along the time dimension, a number of important questions become contextualized and more readily addressable, including determining the effect of putative risk/resilience factors (eg, hypertension, physical activity) on the onset of AD amyloidosis and or AD-associated cognitive decline.

As initial proof-of-concept, the relationships between the estimated amyloid chronicity (ie, duration of amyloid positivity) and markers of tau pathophysiology and cognition were investigated in a late middle-aged, mostly asymptomatic sample. These analyses suggested that those who were amyloid positive for a greater length of time at cognitive baseline exhibited faster rates of cognitive decline during the 7.2 years of cognitive follow-up, and that persons who developed clinical levels of cognitive impairment were estimated to have been A+ for





**FIGURE 4** Entorhinal cortex SUVR: (A) chronological age versus MK SUVR (model reduced sequentially from cubic polynomial to model including only linear age term) and (B) PiB chronicity versus MK SUVR (all three time terms in cubic polynomial were significant). Colors indicate PiB trajectory group (gray = non-accumulators, red = group 2, green = group 3, blue = group 4). Abbreviations: MK, MK-6240; PiB, Pittsburgh compound B; SUVR, standard uptake value ratio

a mean of 15 years longer than those who did not convert to clinical impairment. These intuitive results may partly explain why some studies demonstrate a relationship between A+ status and cognition during the preclinical stage, whereas others do not.<sup>8,38–41</sup>

Similar to relationships with cognition, models including chronicity to explain entorhinal tau tangles improved model fits compared to models with age alone or dichotomous amyloid status. Furthermore, these results suggested a time-lapsed relationship wherein tangles were detectable several years after the detection of pathologic A $\beta$ . In agreement with previous studies, these results support the hypotheses that the level of amyloid tracer binding is reflective of the cumulative process of amyloidosis and that markers of AD pathophysiology and cognition follow a temporal hierarchy. In addition, these results support previous findings that suggest that age is a risk factor for pathophysiology and cognitive decline in AD, but age itself is not a robust predictor of amyloidosis, entorhinal tangles, and thereby, AD state.

The major contribution of this “proof of concept” study is that the trajectory of amyloid accumulation, age at amyloid positivity, and its chronicity can be estimated and used to describe the disease course of amyloidosis. Study limitations include the following. WRAP is a volunteer cohort with over-sampling of participants with a parental history of AD; this results in higher AD-risk characteristics than in the general population. In addition, the sample is younger and more cognitively intact compared to other longitudinal studies of amyloid accumulation; thus, it is unlikely that our exact equations and parameters will generalize to other radiotracers and study samples. As such, replication of this method in different cohorts is needed to determine to what extent this approach is generalizable. If replicable, estimates of amyloid onset and chronicity, such as described here, should be examined in other research contexts to better understand the impact of treatments, preventative measures, and resilience factors during the preclinical phase of AD.

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## CONFLICTS OF INTEREST

[<sup>18</sup>F]MK-6240 precursor and reference standard used in this study were provided by Cerveau Technologies. Dr. Sterling C. Johnson is principal investigator for a separate ongoing study using MK-6240 sponsored by Cerveau Technologies. Dr. Sterling C. Johnson served on an advisory board for Roche Diagnostics in 2018. Dr. Howard Rowley is a consultant for GE HealthCare and has equity interest in Image-MoverMD. None of the other authors has any relevant disclosures.

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## SUPPORTING INFORMATION

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

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