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Does BioAge identify accelerated aging in individuals with bipolar disorder? An exploratory study in the FACE-BD cohort

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Abstract

Background: Individuals with bipolar disorders (BD) have an estimated loss of life expectancy around 10–15 years. Several laboratory-measured biomarkers of accelerated aging exist (e.g., telomere length), however with a questionable transferability to bedside. There is a need for easily and inexpensively measurable markers of aging, usable in routine practice, such as BioAge.

Methods: We calculated BioAge that estimates biological age based on routine blood tests and a physical exam, in a sample of 2220 outpatients with BD. We investigated associations between BioAge Acceleration (BioAgeAccel), which is an indicator of accelerated aging, and sociodemographic variables, clinical variables, and current psychotropic medication use.

Results: Mean chronological age was 40.2 (± 12.9). Mean BioAge was 39.1 (± 12.4). Mean BioAgeAccel was 0.08 (± 1.8). A minority of individuals (15%) had a BioAgeAccel above 2 years. Multivariable analyses suggested strong associations between a higher BioAgeAccel and younger age, male sex, overweight and sleep disturbances.

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Regarding current psychotropic medication use, discrepancies between univariate and multivariate analyses were observed.

Conclusions: A minority of individuals with BD had an accelerated aging as measured by BioAge. We identified associations with potentially modifiable factors, such as higher body mass index and sleep disturbances, that are however nonspecific to BD. These results require replications in independent samples of individuals with BD, and comparisons with a control group matched for age and gender. Longitudinal studies are also required to test whether any change in metabolic health, or sleep might decrease BioAgeAccel.

KEYWORDS

accelerated aging, bioage, biological age, bipolar disorder, determinants, medications, obesity, sleep

1 | INTRODUCTION

The literature has repeatedly demonstrated a risk of premature death in individuals with bipolar disorders (BD). This risk is not only related to suicide or accidents which frequencies are increased in BD as compared with the general population, but is also related to associated medical conditions (mostly cardiovascular diseases).¹ Life expectancy is estimated to be decreased by 10–20 years in BD as compared with the general population.^{1–7} These findings have led to the hypothesis of an accelerated aging in individuals with BD.

Accelerated aging in BD has been mainly explored using laboratory-measured biological markers, mostly telomere length (TL), mitochondrial DNA copy number (mtDNAcn), and epigenetic age (EpiAge). A meta-analysis of 10 studies demonstrated that individuals with BD had shorter TL as compared with controls, whatever their current mood states and whatever the methods used to measure TL.⁸ We have recently shown that individuals with BD had a decrease around 36% of mtDNAcn as compared with healthy controls,⁹ however, results from previous meta-analyses have been inconsistent.^{10,11} Epigenetic age (EpiAge) that is calculated from methylomic data using numerous DNA CpG sites and different calculation algorithms is another marker of cellular aging. EpiAge has been suggested to be significantly increased as compared with chronological age in individuals with BD.^{12,13}

All these biomarkers of accelerated aging have attracted recent and increasing attention in BD¹⁴ and in psychiatry in general. However, they all are laboratory-based measures obtained from blood samples specifically done for research purpose, and therefore not easily implementable in routine practice and clinical settings. Moreover, EpiAge requires substantial costs for methylomic data acquisition, but also bioinformatic resources for calculation. Therefore, the feasibility of a bench to bedside translation remains questionable for these biomarkers and there is a need to identify more easily and inexpensively measurable markers, that can be used in routine practice and clinical settings.

BioAge and PhenoAge may represent such easily and inexpensively measurable markers of accelerated aging. Both are derived from

biological and/or physical measures collected by routine blood tests and a physical exam and therefore are available in clinical practice. To be calculated, both PhenoAge and BioAge include chronological age and levels of albumin, creatinine, C-reactive protein (CRP), alkaline phosphatase, in addition with levels of fasting glucose, red blood cell mean corpuscular volume, red blood cell distribution width (RDW), and white blood cell count for PhenoAge and systolic blood pressure, levels of glycated hemoglobin (HbA1c), and total cholesterol for BioAge. PhenoAge and BioAge have been suggested to predict mortality better than chronological age and both are comparable – when compared with chronological age—for their better predictive sensitivity and strength of association with mortality.^{15,16} In a study including older individuals, biological age was associated with physician-observed morbidity and subjective health, over and above the effects of chronological age, as well as alternative biomarkers including TL or EpiAge.¹⁷ In addition, BioAge acceleration has been suggested to predict future disease onset (e.g., Parkinson's disease, diabetes, and kidney diseases).¹⁸ None of these markers of accelerated aging (PhenoAge or BioAge) have been studied yet in psychiatry. Therefore, their relevance to identify individuals with psychiatric disorders and potential accelerated aging remains unknown.

The aims of this study were (1) to calculate the biological age (BioAge) and the BioAge acceleration in a large sample of 2220 individuals with BD, based on available clinical data (routine blood samples and physical exam) and (2) to characterize which sociodemographic and clinical characteristics of BD were associated with a BioAge acceleration.

2 | MATERIALS AND METHODS

2.1 | Study population

The study sample consisted of individuals who were clinically assessed in the French network of FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) from 2009 to 2020. This

network is supported by the French Ministry of Health and has been developed under the aegis of the nonprofit Fondation FondaMental, to offer standardized, specialized, and personalized care for individuals with BD. All outpatients aged 16 years or older, diagnosed with BD according to DSM-IV criteria (all bipolar subtypes [I, II, and not otherwise specified: NOS])¹⁹ underwent a standardized clinical assessment and were enrolled in the FACE-BD cohort. There are 12 expert centers in France, and all use the same comprehensive clinical assessments, described in detail elsewhere.²⁰ The assessment protocol was approved by the institutional review board (Comité de Protection des Personnes Ile de France IX; January 18, 2010), in accordance with the French laws for non-interventional studies, and data use requires only an information letter that is provided to each participant.

2.2 | Clinical psychiatric assessment

At baseline, a multidisciplinary team (nurses, psychiatrists, and psychologists) interviewed the participants using the SCID²¹ and systematically recorded information related to sociodemographic characteristics, onset and course of BD, and psychiatric comorbidities (anxiety and substance use disorders). Duration of BD was calculated based on age and age at onset. The density of mood episodes was calculated by dividing the sum of lifetime mood episodes (whatever their polarity) by the duration of BD. Current depressive and (hypo)manic symptoms were assessed respectively with the Montgomery Asberg Depression Rating Scale²² and the Young Mania Rating Scale.²³ We assessed subjective sleep quality with the Pittsburgh Sleep Quality Index (PSQI),²⁴ childhood maltreatment with the Childhood Trauma Questionnaire (CTQ),²⁵ chronotype with the Composite Scale of Morningness,²⁶ functioning with the Functioning Assessment Short Test (FAST),²⁷ and adherence to medication with the Medication Adherence Rating Scale (MARS).²⁸ Metabolic syndrome (MetS) was defined according to the criteria of the International Diabetes Federation criteria.²⁹ Current psychotropic treatments (lithium, anticonvulsants, atypical antipsychotics, antidepressants) were recorded.

2.3 | Biological age calculation

PhenoAge calculation could not be calculated in this sample because red blood cell distribution width (RDW) was not measured in routine blood samples in the FACE-BD cohort. Therefore, we used BioAge calculation for which most required data were directly available, except one (HbA1c). Since the database included fasting plasmatic glucose levels, but not HbA1c, this latter parameter was estimated by the following formula: $\text{HbA1c (\%)} = (\text{glucose (mmol/l)} + 2.59) / 1.59$.

Formula for the calculation of BioAge is given in³⁰ (see Data S1—supplementary material for an open access to the formula and calculation methods). All raw values were first converted into the measure

units required for BioAge calculation. Aberrant values (below 1st and 99th percentile) were dropped when appropriate (for instance, 1st percentile of CRP levels was not dropped). As proposed by,³⁰ “BioAge acceleration (BioAgeAccel) was measured with the residuals of regressing BioAge on chronological age. Instead of using the difference between BioAge and chronological age difference, we calculated the residuals from regressing BioAge on chronological age. In this way, the residuals are robust to various normalization methods and measurement platforms.”³⁰ These residuals were used to quantify BioAgeAccel, with positive values indicating that an individual is biologically older than his/her chronological age.

2.4 | Statistical analyses

Normality of distribution of chronological age, BioAge, and BioAgeAccel were inspected using Skewness and Kurtosis values. We used Pearson or Spearman correlation tests to investigate associations between two continuous variables and *t*-tests, Mann-Whitney tests or Kruskal-Wallis tests to investigate associations between categorical and continuous variables.

We then included all variables that were associated with BioAgeAccel in univariable analyses (threshold selected: $p < 0.15$) in a linear regression using BioAgeAccel as the dependent variable. Finally, the same model was run again including all medications prescribed at inclusion and adherence to medication as independent variables. This was performed as a second step of multivariable analyses since the “medication section” of the database was the one with the most missing data. No imputation of data was done. We applied a correction for multiple testing for univariable analyses (Bonferroni correction).

3 | RESULTS

3.1 | Sample characteristics

The sample consisted of 2220 participants. The mean age at inclusion was 40.2 (± 12.9) (range: 16–80). Most participants were females (61.4%) and with high education level (71.2% had at least a bachelor degree). BD type 1 was diagnosed in 45.5% of individuals and BD type 2 was diagnosed in 43.4% of individuals. The participants had a mean age at onset of 23.7 (± 9.4), a mean duration of the illness of 16.7 (± 10.9) and a mean lifetime number of mood episodes of 9.4 (± 9.8). Psychiatric-associated conditions were frequent: lifetime anxiety disorders (47.6%), current tobacco use (46.8%) and lifetime suicide attempts (40.1%). Around one-half of the sample was overweighted (50.2%), 19.1% met the criteria for obesity and 22.5% met the criteria for a metabolic syndrome. Most common psychotropic drugs prescribed at inclusion were anticonvulsants (49.6%) and atypical antipsychotics (42.4%), followed by lithium (32.7%) and antidepressants (38.7%).

Details about the sample are presented in Table S1.

3.2 | Description of chronological age, Bioage, and BioAge Acceleration

Skewness and Kurtosis values were between -1 and $+1$ for both chronological age, BioAge and BioAgeAccel. The mean chronological age was $40.2 (\pm 12.9)$ (range: 16–80). Mean BioAge was $39.1 (\pm 12.4)$ (range: 15–80). Mean BioAgeAccel was $0.08 (\pm 1.8)$ (range: -5.3 to $+7.2$). BioAgeAccel was below -2 (i.e., younger than chronological age) for 11.5% of individuals and above $+2$ (i.e., older than chronological age) for 15.4% of individuals.

There was a positive correlation between chronological age and BioAge (Pearson $\rho=0.99$, $p<0.001$) and a negative correlation between chronological age and BioAgeAccel (Pearson $\rho=-0.14$, $p<0.001$), meaning that younger individuals had higher BioAgeAccel. All parameters used to calculate BioAge significantly correlated with chronological age as presented in Table S2 (including means and standard deviations for all parameters).

3.3 | Associations between BioAge Acceleration, sociodemographic and clinical characteristics of the sample

Associations between available variables and BioageAccel are presented in Table 1. Seven associations remained significant after correction for multiple testing (Bonferroni corrected p -value for 30 tests: $p<0.0016$), that is, associations with age, sex, illness duration, lifetime cannabis misuse, sleep disturbances, CSM score, and indicators of poor metabolic health (whatever its definition, i.e. overweight, obesity or metabolic syndrome). In summary, BioageAccel was higher in younger individuals, in males, in individuals with shorter duration of BD, with greater sleep disturbances, with evening type, and with poor metabolic health.

While not significant after correction for multiple testing, some additional associations were observed. Current smoking, lower age at BD onset, and lifetime history of alcohol use disorders were associated with a higher BioageAccel. Regarding current medications, only a prescription of atypical antipsychotics was associated with a higher BioageAccel. Of note, two associations were not in the expected direction: a lower BioageAccel was observed in individuals with lifetime anxiety disorders and in individuals with childhood maltreatment.

We then included the following variables as independent variables in model 1 with a stepwise option (age, sex, density of mood episodes/year, lifetime anxiety disorders, current smoker, lifetime alcohol use disorders, lifetime cannabis use disorders, YMRS score, PSQI >5 , CSM score, CTQ total score, FAST score, and overweight). In model 2, we used the same approach as in model 1, while adjusting (forced option in the regression model) for all currently used medications and MARS score.

In model 1, associations were found between a higher BioAgeAccel and male sex, younger age, overweight, and sleep disturbances. In model 2 (adjusted for medications and adherence to medications), main associations were found between a higher

TABLE 1 Univariable analyses between clinical variables and BioAgeAccel.

	Rho or mean (\pm SD)	p -values
<i>Sociodemographic characteristics</i>		
Age	-0.14	<0.001
Sex		
Females	-0.23 (1.79)	<0.001
Males	0.57 (1.76)	
Education level (high school level)		
No	0.09 (1.94)	0.81
Yes	0.11 (1.77)	
Living alone		
No	0.08 (1.89)	0.45
Yes	0.14 (1.75)	
<i>Bipolar disorder characteristics</i>		
BD subtype		
BD type I	0.09 (1.82)	0.89
BD type II	0.06 (1.78)	
BD type NOS	0.11 (1.98)	
Age at onset	-0.06	0.006
Illness duration	-0.10	<0.001
Number of mood episodes	-0.03	0.24
Density of mood episodes/year	0.04	0.11
Rapid cycling		
No	0.10 (1.84)	0.67
Yes	0.06 (1.82)	
Lifetime suicide attempt		
No	0.10 (1.82)	0.56
Yes	0.06 (1.83)	
Lifetime anxiety disorders		
No	0.19 (1.84)	0.08
Yes	0.04 (1.84)	
Current smoker		
No	-0.04 (1.79)	0.004
Yes	0.19 (1.86)	
Lifetime alcohol use disorders		
No	0.07 (1.81)	0.04
Yes	0.27 (1.91)	
Lifetime cannabis use disorders		
No	0.04 (1.84)	<0.001
Yes	0.42 (1.78)	
<i>Dimensional assessments</i>		
MADRS score	0.03	0.16
YMRS score	0.03	0.14
PSQI >5		
No	-0.09 (1.82)	<0.001
Yes	0.19 (1.84)	
CSM score	-0.07	0.001

TABLE 1 (Continued)

	Rho or mean (\pm SD)	<i>p</i> -values
CTQ total score	-0.05	0.03
FAST score	0.05	0.10
<i>Metabolic health</i>		
Overweight		
No	-0.43 (1.67)	<0.001
Yes	0.60 (1.83)	
Obesity		
No	-0.16 (1.73)	<0.001
Yes	1.13 (1.83)	
Metabolic syndrome		
No	-0.26 (1.64)	<0.001
Yes	1.42 (1.88)	
<i>Current medications</i>		
Lithium		
No	0.12 (1.90)	0.59
Yes	0.07 (1.74)	
Anticonvulsants		
No	0.19 (1.83)	0.06
Yes	0.02 (1.87)	
Atypical antipsychotics		
No	0.01 (1.87)	0.01
Yes	0.24 (1.82)	
Antidepressants		
No	0.03 (1.79)	0.06
Yes	0.21 (1.94)	
Number of psychotropic drugs	0.02 ^a	0.22
Adherence to medication (MARS)	-0.04	0.10

Abbreviations: BD, Bipolar Disorder; CSM, Composite Scale of Morningness; CTQ, Childhood Trauma Questionnaire; FAST, Functioning Assessment Short Test; MADRS, Montgomery Asberg Depression Rating Scale; MARS, Medication Adherence Rating Scale; PSQI, Pittsburgh Sleep Quality Index; YMRS, Young Mania rating Scale.
^aKendall's tau-b correlation.

Note: In bold, *p*-values significant after correction for multiple testing ($p < 0.0016$).

BioAgeAccel and male sex, younger age, and overweight. To a lesser extent, a higher BioAgeAccel was associated with higher sleep disturbances, and current antidepressant use. Both current lithium use and lifetime anxiety disorders were associated with a lower BioAgeAccel. Results are presented in Table 2A,B.

4 | DISCUSSION

This is the first study to investigate BioAge as an estimate of accelerated aging in individuals with BD. At a group level, individuals with BD had a mean BioAgeAccel of only 0.08 year. Only a minority

of individuals (15.4%) had a BioAgeAccel above 2 years (i.e., older than chronological age). Multivariable analyses identified several variables as being associated with a higher BioAgeAccel, that is, younger age, male sex, overweight, and sleep disturbances. Lifetime presence of anxiety disorders was weakly associated with a lower BioAgeAccel. Regarding current psychotropic medications use, discrepancies were observed between univariate and multivariate analyses, therefore preventing any definite conclusion.

The first result deserves some comments: at a group level, individuals with BD do not seem to present an accelerated aging. While BioAgeAccel ranged from -5.3 to +7.2, mean BioAgeAccel was near 0 and only a minority of individuals had a BioAgeAccel above 2 years (15.4%). As a comparison, when using TL and mtDNA_{cn}, we found that at least one-third of young individuals with BD already had accelerated aging,⁹ a proportion that is far above the one observed when using BioAge. Hence, this observation questions the relevance of the use of BioAge to identify individuals with accelerated aging in BD. BioAge has the advantage of being easily measurable and calculated in routine. However, low agreements have been found between BioAgeAccel, TL, and EpiAge,³¹ and these markers may not measure the same aspects of the aging process. Here, the lack of a control group matched for age and gender is an obvious limitation that precludes to determine whether BioAgeAccel might significantly differ between groups. Further studies are therefore required, including a control group, and possibly extending the investigations to other severe mental disorders.

The second result that deserves some comments is the association between a younger chronological age and a higher BioAgeAccel. This may suggest that some young individuals with BD could be characterized by an accelerated aging, which would be in line with one of our previous studies using TL and mtDNA_{cn}.⁹ However, this association may be only due to a bias. Older individuals with BD and with a high BioAgeAccel might have been not included in this study (possibly referred to other medical services, but not to our psychiatric centers, because of severe medical morbidities). Hence, we cannot exclude truncated data in the oldest population. Further studies using BioAge should be conducted specifically in the youngest population of individuals with BD to test whether accelerated aging might already be observed in these individuals.

Third, we identified strong associations between a higher BioAgeAccel, overweight, and sleep disturbances. Nevertheless, these associations are unlikely to be specific to BD. Obesity has been associated with shorter TL in apparently healthy adults,^{32,33} with acceleration of epigenetic ages in BD,^{13,34} but not with mtDNA_{cn}.³⁵ In parallel, optimal sleep habits may contribute to telomere preservation,³⁶ circadian misalignment may be associated with telomere shortening,³⁷ and while no association was observed between DNA methylation and sleep outcomes in children.³⁸ These studies and the present one may suggest links (nonspecific to BD) between accelerated aging, sleep, and metabolic health. Here, the cross-sectional design of our study does not allow to infer any causality. Studies including both individuals with BD and controls would

	Beta	SE	t	p	VIF
Model 1					
Intercept	1.741	0.226	7.696	<0.001	
Age	-0.028	0.004	-7.856	<0.001	1.034
Sex	-0.718	0.093	-7.728	<0.001	1.036
Overweight	1.033	0.091	11.36	<0.001	1.045
PSQI >5	0.342	0.094	3.641	<0.001	1.061
YMRS	0.022	0.012	1.841	0.066	1.018
Lifetime anxiety disorders	-0.177	0.092	-1.915	0.056	1.074
Model 2					
Intercept	1.976	0.365	5.415	<0.001	
Age	-0.028	0.004	-6.406	<0.001	1.136
Sex	-0.717	0.111	-6.465	<0.001	1.081
Overweight	1.126	0.108	10.427	<0.001	1.075
PSQI >5	0.256	0.111	2.303	0.021	1.101
Lifetime Cannabis use disorders	0.231	0.139	1.659	0.097	1.109
Lifetime anxiety disorders	-0.271	0.109	-2.491	0.013	1.087
Lithium	-0.289	0.121	-2.395	0.017	1.175
Anticonvulsants	-0.192	0.113	-1.706	0.088	1.175
Atypical antipsychotics	-0.009	0.112	-0.083	0.934	1.136
Antidepressants	0.244	0.111	2.209	0.027	1.071
MARS	-0.002	0.029	-0.079	0.937	1.093

Note: In bold: $p < 0.001$, in italic $p < 0.05$.

Abbreviations: MARS, Medication Adherence Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SE, standard error; VIF, variance inflation factor; YMRS, Young Mania rating Scale.

help to clarify the specificity or—more likely—the nonspecificity of these associations to BD. Furthermore, longitudinal studies would help to clarify the causal links between accelerated aging, metabolic health, and sleep disturbances, for instance investigating whether any improvement/worsening in metabolic health and/or sleep quality would decrease/increase BioAgeAccel.

In this study, we did not find any specific variable related to BD as associated with BioAgeAccel (illness duration, density of episodes, or rapid cycling for instance). Regarding the associations between BioAgeAccel and current psychotropic medication use, no firm conclusion can be proposed. Indeed, we observed discrepancies between results obtained in univariate and multivariate analyses. In univariate analyses, we observed an association between a higher BioAgeAccel and current use of atypical antipsychotics, however no longer significant after correction for multiple testing. In multivariate analyses, we observed associations between a lower BioAgeAccel and current use of lithium, and between a higher BioAgeAccel and current use of antidepressants. These results should be taken with great caution for several reasons. First, these associations were weak, no longer significant after correction for multiple testing, and inconsistent between univariate and multivariate analyses. Second, the section “psychotropic medications” in our database had missing data (27% of participants). Finally, we use only the presence or absence of currently prescribed psychotropic

drugs, but without any information about the dosage, plasmatic levels, nor the cumulative duration of exposure which should be considered in future studies. We also did not have information related to lifetime exposure for all psychotropic medications (for instance prescribed in the past, but not anymore at inclusion). Further investigations are therefore needed to conclude whether psychotropic medications might be associated with BioAgeAccel in BD. This would be of particular interest given, for instance, the fact that lithium has been suggested to have some antiaging properties,³⁹ although not consensual in the literature.⁴⁰

This study has several strengths which are mainly the large sample size and the use of an exhaustive clinical characterization of the individuals. However, several limitations should be mentioned. First, the cross-sectional design of this study prevents to infer any causal links, as stated above. Second, we have not considered all possible medical comorbidities (nor associated medications used to treat these), and this will be the purpose of a future study in a larger sample. Third, we did not consider diet or physical activities that may contribute to aging, because of the absence of such data in this sample. Fourth, the sample included only individuals with BD, without any comparison made with other groups of individuals with severe psychiatric disorders (such as schizophrenia for instance), nor with a healthy control group. Finally, we also did not provide any external validation for BioAge in this sample

TABLE 2 Multivariable analyses between clinical variables and BioAgeAccel (Model 1), then adjusted for all medications and adherence to medication (Model 2).

(for instance using other types of markers of accelerated aging, such as TL, mtDNAcn, or EpiAge).

In conclusion, at a group level, BioAge fails to identify a large subgroup of individuals with accelerated aging, thus questioning its relevance in BD. Younger age, male sex, metabolic health, sleep disturbances were associated with higher BioAgeAccel, which is nevertheless unlikely to be specific to BD. These results require independent replications in larger sample of individuals with BD including a control group matched for age and gender, and also require investigations in other types of severe psychiatric disorders. Longitudinal studies would also be of interest to explore the dynamic of BioAgeAccel at different timepoints and whether any change in metabolic health, or sleep quality might be associated with any modification of BioAgeAccel.

AUTHOR CONTRIBUTIONS

O.G, C.M-C., and B.E. managed the literature searches and the statistical analyses, interpreted the results and wrote the manuscript. All other authors contributed to data collection, proposed a critical review of the manuscript, and approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (BE), upon reasonable request.

ETHICS STATEMENT

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The follow-up protocol was approved by the institutional review board (Comité de Protection des Personnes Ile de France IX; 18 January 2010). In accordance with the French laws for non-interventional studies and according to the Ethical Committee, the study participation requires only an information letter since the clinical data were collected as part as the usual medical care system in France.

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SUPPORTING INFORMATION

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

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