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BRIEF REPORT

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# Interaction between APOE ε4 status, chemotherapy and endocrine therapy on cognitive functioning among breast cancer survivors: the CANTO-Cog longitudinal study

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## Abstract

**Background** Apolipoprotein ε4 genotype (APOE4) has been associated with cancer-related cognitive impairment, but its interaction with treatments remains unclear. This longitudinal study aims to evaluate the association between APOE4 and cognitive impairment in women with breast cancer (BC) undergoing chemotherapy (CT) or endocrine therapy (ET).

**Findings** Patients with stage I–III breast cancer completed cognitive tests at diagnosis (before surgery), then at year-1, year-2, and year-4 post-diagnosis. APOE4 status (APOE4+ [carriers] vs. APOE4– [non-carriers]) was genotyped from blood sample. Cognitive outcomes included episodic memory, working memory, attention, processing speed, and executive functions. Patients were defined as having overall cognitive impairment if ≥ 2 domains were impaired. We fitted logistic and linear mixed models to assess associations of APOE4 status with cognitive impairment over time and interactions of APOE4 with CT and ET. Among 334 patients, 64 (19%) were APOE4+, 117 (35%) patients were treated with CT, 41 (12%) with ET, and 162 (49%) with CT+ET. There were no significant association between overall cognitive impairment and APOE4, nor interactions with CT or ET. At year-4, APOE4+ patients treated with ET had lower attention performance than APOE4– patients not treated with ET, and APOE4+ patients not treated with ET had lower episodic memory performance than APOE4– patients not treated with ET.

**Conclusions** This study suggests APOE4 genotyping is ineffective for detecting cognitive impairment in BC. New genotypes should be identified to predict cognitive decline in BC.

**Keywords** Breast cancer, APOE4, Cancer-related cognitive impairment, Endocrine therapy, Chemotherapy

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## Introduction

Cancer-related cognitive impairment (CRCI) describes transient, mild cognitive symptoms in individuals with cancer. CRCI affects around 30% of breast cancer (BC) patients either before or after treatments [1, 2]. Among the various risk factors associated with CRCI, biomarkers have been the subject of investigation, with a particular focus on genetic predisposition [3–5]. In the present study we assessed the association of the Apolipoprotein E genotype, specifically the Ɛ4 polymorphism (APOE4) with CRCI. APOE4, a risk factor of accelerated cognitive aging [6] and Alzheimer's disease [7], could impact key biological mechanisms associated with CRCI, including blood–brain barrier integrity and neurogenesis [8]. APOE4 reduces antioxidant activity, while cancer causes oxidative stress. Oxidative stress speeds cognitive decline, so cancer may accelerate brain ageing and increase CRCI risk in APOE4 patients after treatment [9].

Some studies link APOE4 to CRCI [10, 11], but the interaction with other factors may also play a role [9, 12]. Smoking provides protection against a deficit in the nicotine receptor associated with APOE4+ genotyping, thereby increasing the number of neurotransmitter bursts required for optimal cognitive functioning [12, 13]. Chemotherapy [14] and endocrine therapy [9, 15] have been linked to a greater prevalence of cognitive decline in patients APOE4+. Despite being overlooked in the context of CRCI, it appears that postmenopausal patients APOE4+ may be at an elevated risk of cognitive decline [16].

This longitudinal study aims to examine the association between APOE4 and cognitive functioning in BC patients, as well as the interactions between APOE4 and CT or ET, while controlling for the effects of smoking and menopausal status.

## Methods

This study used genomic data from the prospective CANcer TOxicity cohort (CANcer TOxicities, ClinicalTrials.gov identifier: NCT01993498, study registration date 2013-10-17) and cognitive data from the sub-study CANTO-Cog (eight CANTO centres; recruitment from April 2014 to September 2018). All participants in the CANTO-Cog sub-study provided written informed consent and the study was approved by the ethics committee (ID-RCB:2011-A01095-36,11-039). Eligible patients were women newly diagnosed with localized, stage I–III BC who had received no cancer treatment, including surgery for current BC (see Lange et al., 2020 for detailed inclusion criteria [1]). Patients were evaluated at diagnosis (baseline) and during follow-up visits at year-1, year-2, and year-4 (i.e. around 3 years after ET initiation) post-diagnosis. At each time point, a neuropsychological battery was administered (for further details see Lange et al. [1]). Scores were corrected for practice effect, transformed into z-scores, and aggregated in the following domains: episodic memory, working memory, processing speed, attention, and executive function. Cognitive impairment of each domain was determined according to ICCTF recommendations [17] (e.g. at least two tests z-scores $\leq -1.5$ or one single test z-score $\leq -2.0$). If at least two domains were impaired, patients were categorized with overall cognitive impairment. A blood sample was realised at baseline. Genomic data were genotyped twice from baseline blood sample using Illumina Chips (GSAMDv1.0 & v3.0 and InfiniumExomev1.1). The quality of the genotyping data was controlled with PLINK software: SNPs and individuals with high levels of missingness (> 2%) were deleted. Samples with sex discrepancy, unusual heterozygosity rate (> 3sd from the mean), parent–offspring relations were removed. SNPs that were not in Hardy Weinberg equilibrium (pv < 1e−10) were removed. Missing genotypes were then imputed against the 1000 genome dataset using shapeit2 and minimac4 softwires.

APOE4 status was determined with the rs429358 and rs7412 genotypes. APOE4 carriers (APOE4+, Ɛ4/Ɛ4 and Ɛ3/Ɛ4) were differentiated from non-carriers (APOE4−).

### Statistical analyses

For analysis, patients were categorized as two distinct groups: APOE4+ and APOE4−. Descriptive statistics for the socio-demographic and clinical variables were generated for each group, and compared using the t test, Wilcoxon test, $\chi 2$ test, or Fisher's exact test, as appropriate.

To investigate the interaction between APOE4 and treatments, APOE4+ and APOE4− groups were categorized based on CT or ET status, distinguishing between treated (CT+ or ET+) and untreated (CT− or ET−) patients. To measure the association between APOE4 and overall cognitive impairment, as well as the interactions with CT, and ET, logistic models were fitted at each timepoint. Furthermore, repeated measures linear mixed models were fitted for each cognitive domain over time. All multivariate models were adjusted for age, level of education, smoking status, menopausal status, cognition at baseline, and when appropriate, CT and/or ET.

## Results

A total of 334 patients were included in the analysis (Fig. 1).

Table 1 shows the baseline demographic and clinical characteristics of the patients in the study. There were no significant differences between included and excluded patients (Additional file 1). In the whole group, 117 (35%) patients were treated with CT, 41 (12%) were treated with

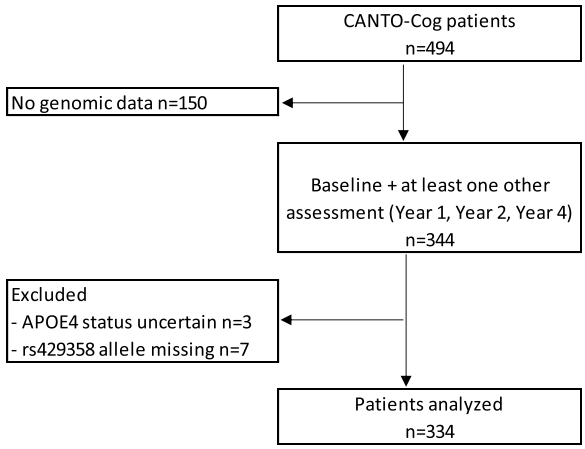


**Fig. 1** Flow chart

**Table 1** Sociodemographic and clinical characteristics of patients at baseline (prior treatment) and treatments at follow-up

| | Total n = 334 | APOE4− n = 270 | APOE4+ n = 64 | *p* value |
|---|---|---|---|---|
| Age, mean ± SD | 53.9 ± 11 | 54.3 ± 11 | 52.1 ± 10 | 0.13 |
| Years 65+, n (%) | 53 (16) | 44 (16) | 9 (14) | |
| Years 70+, n (%) | 21 (6) | 17 (6) | 4 (6) | |
| Years of school, mean ± SD | 13.3 ± 2.7 | 13.2 ± 2.6 | 13.8 ± 3.1 | 0.17 |
| Smoking status, n (%) | | | | 0.46 |
| Ever | 182 (54) | 144 (53) | 38 (59) | |
| Never | 152 (46) | 126 (47) | 26 (41) | |
| Menopausal status, n (%) | | | | 0.25 |
| Pre | 173 (52) | 135 (50) | 38 (59) | |
| Post | 159 (48) | 133 (50) | 26 (41) | |
| Missing | 2 (< 1) | 2 (< 1) | 0 (0) | |
| Cancer stage, n (%) | | | | 0.8 |
| Stage I | 149 (45) | 120 (45) | 29 (45) | |
| Stage II | 144 (43) | 115 (43) | 29 (45) | |
| Stage III | 39 (12) | 33 (12) | 6 (10) | |
| Missing | 2 (< 1) | 2 (< 1) | 0 (0) | |
| Radiation therapy, n (%) | 312 (93) | 250 (93) | 62 (97) | 0.34 |
| Chemotherapy, n (%) | 203 (61) | 167 (62) | 36 (56) | 0.49 |
| Endocrine therapy, n (%) | 279 (84) | 227 (84) | 52 (81) | 0.72 |

ET only, and 162 (49%) BC patients were treated with CT and ET. Sixty-four (19%) APOE4+ and 270 (81%) APOE4− patients were analysed. No significant differences in characteristics were observed between the two groups (Table 1).

The percentage of cognitive impairment for each APOE4 group is available in Fig. 2.

Logistic models demonstrated no significant association between overall cognitive impairment and APOE4 status, nor significant interactions between APOE4 and CT or ET, at any time point (Table 2).

Linear mixed models showed no statistically significant association between cognitive domains and APOE4 status across time points (see Additional files 2 and 3). After treatments, an interaction between APOE4 and ET was observed with regard to episodic memory and attention performance (Fig. 3 and Additional file 4). At year-1, patients APOE4+/ET− had lower episodic memory performance than APOE4− patients, treated ($p_{APOE4-/ET+}=0.01$) or not ($p_{APOE4-/ET-}=0.04$) with ET. At year-2, patients APOE4+/ET− had lower episodic memory performance than all other groups ($p_{APOE4-/ET-}=0.01$, $p_{APOE4-/ET+}=0.04$, $p_{APOE4+/ET+}=0.04$). Finally, at year-4, patients APOE4−/ET− had higher episodic memory performances than patients APOE4+ not treated with ET ($p_{APOE4+/ET-}=0.04$) and higher attention performances than patients APOE4+ treated with ET ($p_{APOE4+/ET+}=0.04$).

## Discussion

This study found no link between APOE4 and CRCI, nor interaction between APOE4 and CT. However, around 3 years after ET, APOE4+/ET+ patients had worse attention than APOE4−/ET− patients, and the latter had better episodic memory.

The proportion of individuals with cognitive impairment did not differ between APOE4 groups, which is consistent with findings from previous studies on CRCI [11]. This finding may be partially attributed to the limited sensitivity of the binary categorisation of CRCI [17, 18]. Despite the use of linear mixed models, no association was identified between APOE4 and cognitive functioning by domain. These results provide evidence that, despite the established role of APOE4 as a risk factor for cognitive decline, it may not be a reliable predictive marker for CRCI, as observed in Alzheimer's disease [19].

No significant interaction between APOE4 and CT was shown. Contrary to the prevailing view on the impact of APOE4 and CT on brain structure and accelerated aging [6, 8], this lack of interaction has been observed in previous studies of smaller samples of BC patients, ranging from 1 month to several years after treatment [15, 20, 21]. Patients with the APOE4+ genotype who were treated with CT exhibited enhanced memory function for up to 1 year following the initiation of ET [9]. The present study found no evidence that APOE4 status was linked to the impact of long-term CT on cognition.

The association of APOE4 with cognition differs depending on whether patients were treated with ET. Patients with the APOE4+ genotype who were not treated with ET had lower episodic memory performance following CT and/or radiation treatments

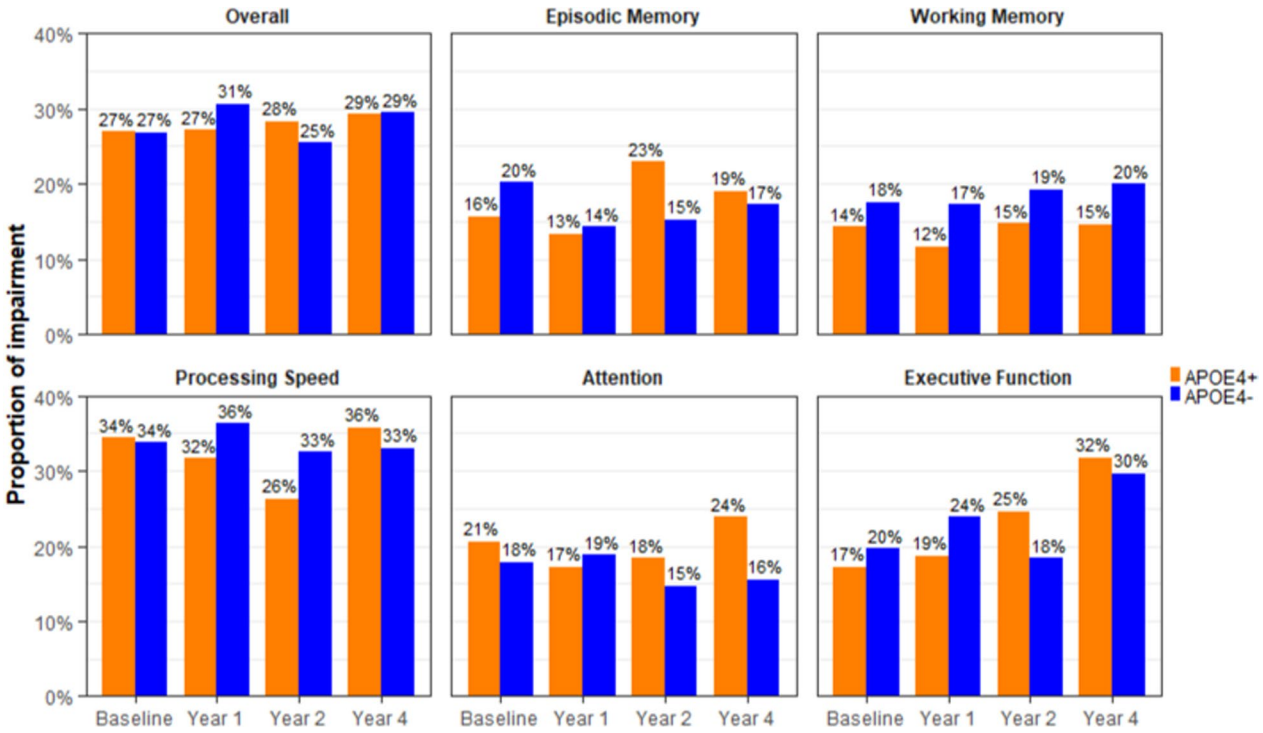


**Fig. 2** Percentage of patients with an overall cognitive impairment and impaired cognitive domain according to APOE4 status. Note: no significant difference was observed

**Table 2** Overall cognitive impairment according to APOE4 status and interactions with chemotherapy and endocrine therapy

| | Baseline | | | Year-1 | | | Year-2 | | | Year-4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* | OR | 95% CI | *p* | OR | 95% CI | *p* | OR | 95% CI | *p* |
| APOE4 | 1.1 | 0.55–2.13 | 0.77 | 0.89 | 0.37–2.02 | 0.78 | 1.2 | 0.49–2.78 | 0.69 | 1.13 | 0.41–2.97 | 0.8 |
| APOE4 × CT | 1.24 | 0.32–4.84 | 0.75 | 1.5 | 0.27–8.69 | 0.64 | 0.72 | 0.12–4.13 | 0.71 | 2.71 | 0.37–21.1 | 0.33 |
| APOE4 × ET | 0.86 | 0.16–5.11 | 0.88 | 1.18 | 0.15–10.6 | 0.88 | 1.4 | 0.12–19.5 | 0.8 | 0.11 | 0.01–1.22 | 0.07 |

Each line is the result of a different logistic model

APOE4, Apolipoprotein Ɛ4 isoform status; CT, chemotherapy status; ET, endocrine therapy status; OR, odds ratio; *p*, *p* value; 95% CI, 95% confidence interval

(year-1 to year-4). Since ET affects episodic memory, patients with APOE4+ who received ET were expected to perform worse [22]. In order to avoid overinterpretation, it is essential to confirm or refute these results using a larger sample of patients. However, we did observe a clinically interesting pattern: the APOE4−/ET− patients performed better than the other groups on episodic memory. Although not all of these results were significant, they are consistent with our hypothesis that the APOE4−/ET− would be a population at lower risk of memory decline.

In accordance with the findings of Van Dyk et al., no negative correlation was found between cognitive functioning and APOE4+ patients until 2 years after diagnosis, but changes were identified in the attention domain after 4 years. [15]. As CRCI is defined as a transient mild cognitive decline that occurs during cancer and its treatments, APOE4 does not appear to be a suitable genotype for predicting risk of CRCI before treatment.

### Limits and strengths

The statistical power was limited by the small sample of patients APOE4+. The strength of our study resides in its prospective long-term longitudinal design which allowed evaluating the role of APOE4 from before any treatment, even surgery, to 4 years after diagnosis. In addition, we

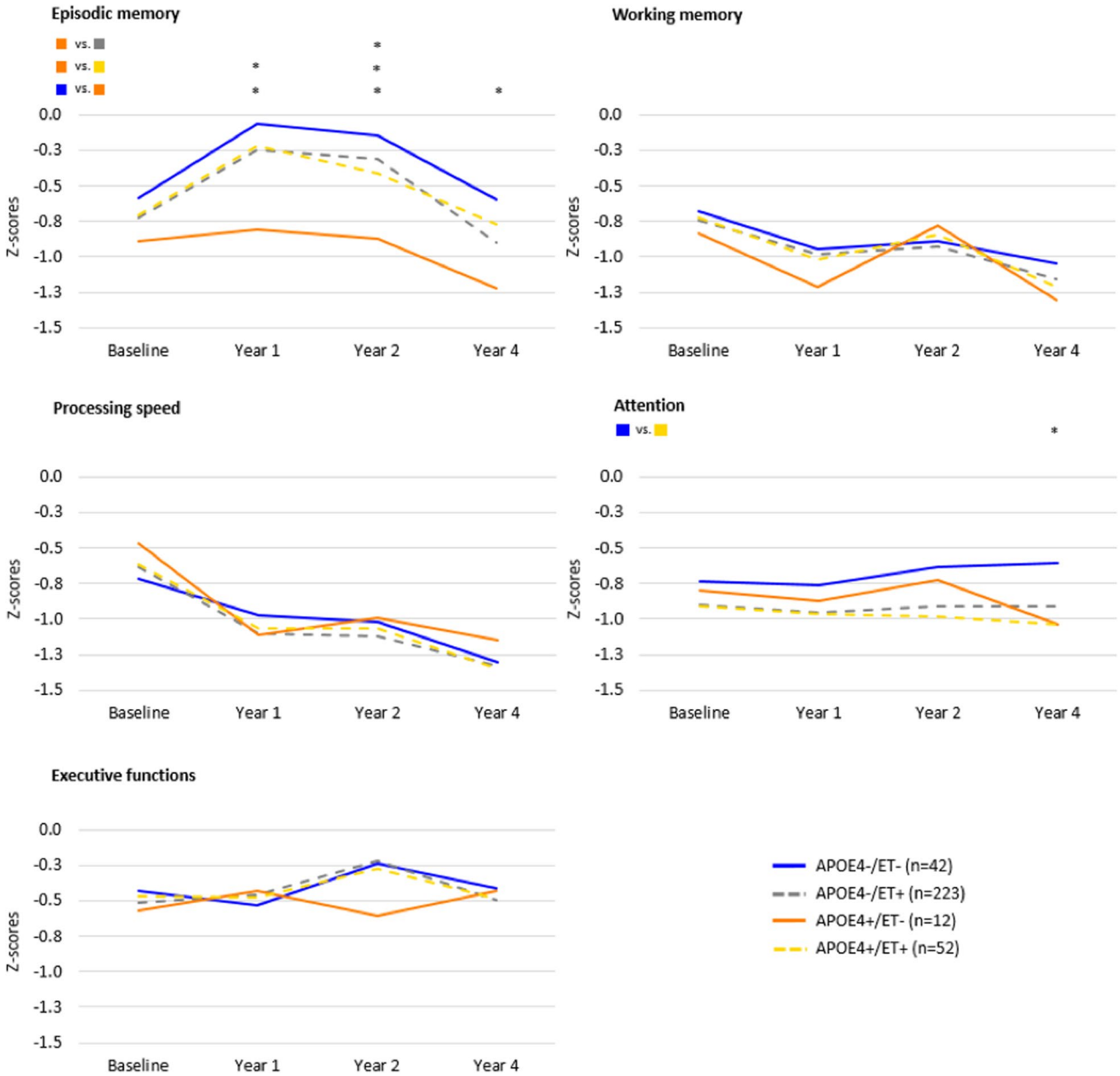


**Fig. 3** Cognitive changes according to APOE4 and ET status (linear mixed models. *: *p* value < 0.05). *Note*: models were adjusted for age (< 50, 50–70, > 70 years old), level of education (< 10 years, 10-12 years, > 12 years), smoking status (ever, never), menopausal status, chemotherapy, and cognition at baseline

controlled our analyses for menopausal and smoking status known to mediate APOE4 effect.

## Conclusion

The present study suggests that APOE is not linked to the effect of CT on cognition, but patients with APOE4−/ET− may have a reduced incidence of post-treatment memory impairment. Our findings also underscore the necessity for the identification of alternative, more accurate genotypes. This is crucial for differentiating patients who are at an elevated risk of developing CRCI prior to the initiation of treatment.

**Abbreviations**

| | |
|---|---|
| APOE4 | Apolipoprotein ε4 isoform |
| BC | Breast cancer |
| CANTO-Cog | Cognitive substudy of CANcer TOxicities |
| CRCI | Cancer related cognitive impairment |
| CT | Chemotherapy |
| ET | Endocrine therapy |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-025-01974-2.

Additional file 1: Socio-demographic and clinical characteristics of included vs. excluded patients.

Additional file 2: Graphics of mixed models of APOE4 effect.

Additional file 3: Graphics of mixed models of APOE4 x Chemotherapy effect.

Additional file 4: Results of mixed models of APOE4 x endocrine therapy.

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**Author contributions**
MD, IVL, ML, FJ, PG, KVD, HC, ADM were involved in the conception and design of the study. FC, ET, SB, JL, CG, DD were involved in project administration, management and/or analysis of data. OR, CB, CL, FL, ML were involved in patients' recruitment and data acquisition. MD wrote the original draft, and all authors commented and/or approved the submitted version.

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**Availability of data and materials**
The datasets used and/or analysed during the current study are available from c-gaudin@unicancer.fr on reasonable request.

## Declarations

**Ethics approval and consent to participate**
All participants provided written informed consent and the study was approved by the ethics committee (ID-RCB:2011-A01095-36,11-039).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's Note