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# Development and Validation of a Predictive Model of Severe Fatigue After Breast Cancer Diagnosis: Toward a Personalized Framework in Survivorship Care

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abstract

**PURPOSE** Fatigue is common and troublesome among breast cancer survivors; however, limited tools exist to predict its risk.

**PATIENTS AND METHODS** Participants with stage I-III breast cancer were prospectively included from CANTO (ClinicalTrials.gov identifier: [NCT01993498](https://clinicaltrials.gov/ct2/show/study/NCT01993498)), collecting longitudinal data at diagnosis (before the initiation of any cancer treatment) and 1 (T1), 2 (T2), and 4 (T3) years after diagnosis. The main outcome was severe global fatigue at T2 (score  $\geq 40/100$ , European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30). Analyses at T3 were exploratory. Secondary outcomes included physical, emotional, and cognitive fatigue (EORTC Quality of Life Questionnaire-FA12). Multivariable logistic regression models retained associations with severe fatigue by bootstrapped Augmented Backward Elimination. Validation methods included 10-fold internal cross-validation, overoptimism-corrected area under the receiver operating characteristic curves, and external validation.

**RESULTS** Among 5,640, 5,000, and 3,400 patients at T1, T2, and T3, respectively, the prevalence of post-treatment severe global fatigue was 35.6%, 34.0%, and 31.5% in the development cohort. Retained risk factors for severe global fatigue at T2 were severe pretreatment fatigue (adjusted odds ratio  $\nu$  no 3.191 [95% CI, 2.704 to 3.767]); younger age (for 1-year decrement 1.015 [1.009 to 1.022]), higher body mass index (for unit increment 1.025 [1.012 to 1.038]), current smoking behavior ( $\nu$  never 1.552 [1.291 to 1.866]), worse anxiety ( $\nu$  noncase 1.265 [1.073 to 1.492]), insomnia (for unit increment 1.005 [1.003 to 1.007]), and pain at diagnosis (for unit increment 1.014 [1.010 to 1.017]), with an area under the receiver operating characteristic curve of 0.73 (95% CI, 0.72 to 0.75). Receipt of hormonal therapy was a risk factor for severe fatigue at T3 ( $\nu$  no 1.448 [1.165 to 1.799]). Dimension-specific risk factors included body mass index for physical fatigue and emotional distress for emotional and cognitive fatigue.

**CONCLUSION** We propose a predictive model to assess fatigue among breast cancer survivors, within a personalized survivorship care framework. This may help clinicians to provide early management interventions or to correct modifiable risk factors and offer more tailored monitoring and education to patients at risk of severe post-treatment fatigue.

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## INTRODUCTION

Cancer-related fatigue is one of the most distressing and common post-treatment *sequelae* among survivors of early-stage breast cancer.<sup>1-3</sup> More than 30% of patients with breast cancer experience persistent fatigue symptomatology up to 10 years after treatment completion.<sup>4-7</sup> Cancer-related fatigue can result in substantial adverse physical, psychosocial, and socioeconomic consequences, having a negative impact

on overall quality of life.<sup>6</sup> Nevertheless, fatigue is still rarely discussed or proactively managed.<sup>8-10</sup> Cancer-related fatigue is multidimensional in its manifestation, involving physical, emotional, and cognitive dimensions, and most likely multifactorial, being determined by multiple patient characteristics and contextual, psychosocial, and behavioral factors, comorbid conditions, and biologic factors including inflammation, disease characteristics, and antineoplastic therapies.<sup>3</sup>

## ASSOCIATED CONTENT

### Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

This study aimed at identifying patients who have an increased risk of severe and persistent post-treatment fatigue 2 years after diagnosis of early-stage breast cancer.

### Knowledge Generated

More than one-in-three patients endured persistent severe post-treatment fatigue. Younger age, higher body mass index, smoking behavior, and concomitant symptom clusters including pretreatment fatigue, anxiety, insomnia, and pain emerged as key risk factors for the development of severe fatigue 2 years after diagnosis. Exploratory models identified receipt of hormonal therapy as an additional risk factor for severe fatigue 4 years after diagnosis.

### Relevance

We propose predictive models that may help clinicians to better assess fatigue at diagnosis of breast cancer and provide timely management interventions to those experiencing severe pretreatment fatigue. Our models may also aid the prompt identification of modifiable risk factors and raise awareness to recognize early signs and act timely on worsening symptoms in patients at long-term risk of severe post-treatment fatigue.

Current knowledge of the long-term prevalence, trajectory, and risk factors of breast cancer–related fatigue is still limited,<sup>4,6,11</sup> which hampers our ability to capture its complexity and variability and to clearly identify those at risk of severe fatigue to potentially target with effective interventions. The prospective multicenter CANcer TOxicity (CANTO) cohort (ClinicalTrials.gov identifier: [NCT01993498](#)) aims at characterizing toxicities of breast cancer, building on an extensive longitudinal collection of clinical, behavioral, tumor, treatment, and patient-reported outcome data.<sup>12</sup> In this study, we used CANTO to develop and validate a risk model and to generate a predictive tool for long-term severe fatigue.

## PATIENTS AND METHODS

### Study Design and Patient Selection

We included CANTO participants with stage I-III breast cancer. CANTO collects data at diagnosis of breast cancer (ie, before the initiation of any cancer treatment) and then at 1 (T1), 2 (T2), and 4 (T3) years after diagnosis (corresponding to approximately 3-6 months, 1 year, and 3 years after primary treatment completion, respectively, including breast surgery, chemotherapy and/or radiation therapy). The CANTO study design (ClinicalTrials.gov identifier: [NCT01993498](#)) was previously described.<sup>12</sup> All patients provided written informed consent. The study was approved by the ethics committee (ID-RCB:2011-A01095-36,11-039).

### Outcome Assessment

The primary outcome of interest was global fatigue, assessed using the multi-item scale of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30<sup>13-15</sup>. Item 10—Did you need to rest? Item 12—Have you felt weak? Item 18—Were you tired? Patients reported fatigue levels on a 4-point

Likert scale per item (response values: 1, not at all; 2, a little; 3, quite a bit; and 4, very much). Responses were converted to a 0-100 scale using a standard scoring algorithm,<sup>15</sup> as follows:

$$\text{Raw Fatigue Score} = \frac{(\text{Score Item 10} + \text{Score Item 12} + \text{Score Item 18})}{\text{No. of Items contributed to the scale (No. = 3)}}$$

$$\text{Standardized Fatigue Score} = \frac{(\text{Raw Score} - 1)}{\text{Range\$}} * 100,$$

\$ is the difference between maximum and minimum possible values of Raw Score. Most items of the EORTC QLQ-C30, including the three items contributing to the global fatigue scale, are scored 1-4, and therefore, the range equals 3.

As secondary outcomes, we assessed the physical, emotional, and cognitive dimensions of fatigue, evaluated by EORTC QLQ-FA12.<sup>16</sup> This is a multidimensional instrument measuring fatigue to be used in conjunction with the core EORTC QLQ-C30. The questionnaire includes five items for physical fatigue (items 1-5), three for emotional fatigue (items 6-8), and two for cognitive fatigue (items 9-10; Data Supplement, online only). In accordance with the scales of the EORTC QLQ-C30, the FA12 scores are transformed to the range of 0-100, following the same scoring algorithm.

For symptom scales, including fatigue, a higher score represents a higher level of symptomatology and/or problems. All standardized fatigue scores were dichotomized using a threshold of  $\geq 40/100$ ,<sup>6</sup> indicating clinically relevant fatigue likely affecting patient's daily life and limiting usual activities, therefore requiring dedicated clinicians' attention and prompting supportive care needs.<sup>6,17-20</sup>

## Other Variables of Interest

Candidate predictors were selected on the basis of clinical expertise and previous evidence of association with fatigue<sup>3,6</sup> and included clinical features, treatment-related factors, and symptoms (including pretreatment fatigue), defined as in [Table 1](#).<sup>21-24</sup>

## Statistical Analysis

**Cohort and outcome description.** Descriptive statistics summarized distribution of predictors and prevalence of severe fatigue at T1, T2, and T3 in the overall cohort.

**Model development.** Patients from the 2012 to 2015 enrollment period of the CANTO study were included in the development cohort according to the availability of global fatigue assessments ( $n = 5,640$  at T1,  $n = 5,000$  at T2, and  $n = 3,400$  at T3; complete case; Data Supplement). Potential predictors of severe fatigue were tested in multivariable logistic regression models, using a bootstrapped ( $N = 100$ ) Augmented Backward Elimination procedure. Variable selection combines backward elimination on the basis of significance ( $P < .05$ ) and the change-in-estimate criterion, so that nonsignificant variables are retained if their exclusion leads to a relevant change in the parameter estimates of other variables in the model.<sup>25</sup> The main prediction analysis focused on the risk of severe global fatigue at year 2 (T2) after diagnosis. Risk assessment at year 4 (T3) was considered exploratory. We evaluated the discrimination ability of the model by C-statistics, calculating the area under the receiver operating characteristic curve (AUC).

**Internal validation.** The model was internally validated using 10-fold internal cross-validation and plotting the observed and estimated probability of severe fatigue for each model.<sup>26</sup> To estimate how well the model would perform in external data sets, an overoptimism penalty was subtracted from the C-statistic of the final model.<sup>27</sup>

**External validation.** Model performance was externally assessed in a validation cohort from a subsequent CANTO enrollment period that extended until 2017 ( $n = 2,461$  at T1,  $n = 2,101$  at T2, and  $n = 1,469$  at T3; Data Supplement). Models previously fitted in the development cohort, including all predictors retained by Augmented Backward Elimination, were applied to patients in the validation cohort. Predictive performance was evaluated by the C-statistic and visually exploring model calibration.

**Fatigue risk prediction.** To obtain a final, parsimonious model, we fit a logistic regression including a set of predictors retained in the development cohort, which were consistent in the validation cohort.

**Sensitivity analyses.** A sensitivity analysis was conducted including patients who responded to global fatigue assessments at all time points.

**Power considerations.** Procedures to calculate the sample size required to obtain a satisfactory outcome prediction were previously published.<sup>28</sup> Briefly, with a binary outcome

prevalence of 31%-35%, a minimal sample size of 998 patients was needed to minimize overfitting (expected shrinkage of predictor effects 10% or lower) and to ensure precise estimation of key parameters in the prediction model at T1 (including an absolute difference of 0.05 in the model apparent and adjusted  $R^2$  value). To achieve the same criteria at T2 and T3, at least 665 and 659 participants were required, respectively.<sup>28</sup> To maximize power, model performance was assessed among all patients who had global fatigue assessments available at T1, T2, and T3, respectively.

This study followed the TRIPOD<sup>29</sup> Checklist for Prediction Model Development and Validation. Additional methodological details are provided in the Data Supplement.

Statistical analysis was performed using SAS statistical software Version 9.4. Statistical significance was defined with a two-sided  $P < .05$ .

## RESULTS

### Primary Outcome Evaluation: Severe Global Fatigue

Characteristics of the overall population are shown in [Table 1](#) and in the Data Supplement by severe global fatigue.

In the development and validation cohorts, respectively, prevalence of severe global fatigue at baseline was 24.3% and 26.7%, reached 35.6% and 38.0% at T1 (ie, closest to primary treatment completion), was substantially unchanged to 34.0% and 35.1% at T2, and remained elevated at 31.5% and 35.9% until T3 ([Fig 1](#)).

Reporting severe pretreatment fatigue was a consistent predictor of post-treatment fatigue at all time points ([Tables 2 and 3](#); Data Supplement).

In the main predictive model for severe global fatigue at T2, six other predictors were consistent in the development and validation models. These included younger age (adjusted odds ratio for 1-year decrement 1.015 [95% CI, 1.009 to 1.022]), higher body mass index (BMI; for unit increment 1.025 [1.012 to 1.038]), current smoking behavior ( $v$  never 1.552 [1.291 to 1.866]), and concomitant symptoms at diagnosis such as worse anxiety ( $v$  noncase 1.265 [1.073 to 1.492]), insomnia (for unit increment 1.005 [1.003 to 1.007]), and pain (for unit increment 1.014 [1.010 to 1.017]; [Table 2](#); AUC 0.73 [95% CI, 0.72 to 0.75]).

In the exploratory model for fatigue at T3, premenopausal status ( $v$  postmenopausal 1.325 [1.123 to 1.563]) and receipt of hormonal therapy ( $v$  no 1.448 [1.165 to 1.799]) surfaced as risk factors for severe fatigue ([Table 3](#); AUC 0.71 [95% CI, 0.70 to 0.72]). Of note, 38.6% and 87.4% of premenopausal women age  $< 40$  and 40 years or older, respectively, reported post-chemotherapy interruption of menses at T3 ( $< 5\%$  overall received ovarian function suppression), which was not associated with severe fatigue ( $P = .914$  and  $P = .515$ , respectively).

Among treatment-related variables, although the development model retained an association between the receipt

**TABLE 1.** Distribution of Cohort Characteristics at 2 Years and 4 Years After Diagnosis, No. (%)

| Characteristic                      | T2, 2 Years After Diagnosis       |                                  | T3, 4 Years After Diagnosis       |                                  |
|-------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
|                                     | Development Cohort<br>(n = 5,000) | Validation Cohort<br>(n = 2,101) | Development Cohort<br>(n = 3,400) | Validation Cohort<br>(n = 1,469) |
| Clinical factors                    |                                   |                                  |                                   |                                  |
| Age at diagnosis, years             |                                   |                                  |                                   |                                  |
| Mean (SD)                           | 56.3 (11.2)                       | 56.4 (10.6)                      | 56.7 (10.9)                       | 55.6 (10.6)                      |
| Minimum-maximum                     | 22.0-88.0                         | 25.3-83.9                        | 22.0-88.0                         | 25.3-83.9                        |
| BMI at diagnosis, kg/m <sup>2</sup> |                                   |                                  |                                   |                                  |
| Mean (SD)                           | 25.8 (5.3)                        | 25.9 (5.4)                       | 25.8 (5.2)                        | 25.6 (5.3)                       |
| Missing                             | 16                                | 8                                | 12                                | 3                                |
| Menopausal status                   |                                   |                                  |                                   |                                  |
| Premenopausal                       | 1,827 (37.2)                      | 786 (37.8)                       | 1,180 (35.4)                      | 595 (40.9)                       |
| Postmenopausal                      | 3,085 (62.8)                      | 1,291 (62.2)                     | 2,155 (64.6)                      | 858 (59.1)                       |
| Missing                             | 88                                | 24                               | 65                                | 16                               |
| Charlson comorbidity index          |                                   |                                  |                                   |                                  |
| 0                                   | 3,705 (80.0)                      | 1,600 (82.9)                     | 2,551 (80.7)                      | 1,151 (83.6)                     |
| ≥ 1                                 | 926 (20.0)                        | 329 (17.1)                       | 612 (19.3)                        | 225 (16.4)                       |
| Missing                             | 369                               | 172                              | 237                               | 93                               |
| Marital status                      |                                   |                                  |                                   |                                  |
| Not partnered                       | 1,223 (26.3)                      | 411 (20.5)                       | 814 (25.8)                        | 284 (19.9)                       |
| Partnered                           | 3,429 (73.7)                      | 1,597 (79.5)                     | 2,339 (74.2)                      | 1,145 (80.1)                     |
| Missing                             | 348                               | 93                               | 247                               | 40                               |
| Education level                     |                                   |                                  |                                   |                                  |
| Primary school                      | 692 (14.6)                        | 231 (11.6)                       | 492 (15.3)                        | 135 (9.5)                        |
| High school                         | 2,224 (46.9)                      | 923 (46.2)                       | 1,508 (46.7)                      | 672 (47.3)                       |
| College or higher                   | 1,821 (38.4)                      | 842 (42.2)                       | 1,226 (38.0)                      | 613 (43.2)                       |
| Missing                             | 263                               | 105                              | 174                               | 49                               |
| Household income, Euros per month   |                                   |                                  |                                   |                                  |
| < 1,500                             | 640 (14.5)                        | 248 (12.4)                       | 425 (14.2)                        | 153 (10.8)                       |
| ≥ 1,500 to < 3,000                  | 1,768 (40.2)                      | 861 (43.1)                       | 1,199 (40.0)                      | 572 (40.4)                       |
| ≥ 3,000                             | 1,992 (45.3)                      | 888 (44.5)                       | 1,372 (45.8)                      | 691 (48.8)                       |
| Missing                             | 600                               | 104                              | 404                               | 53                               |
| Alcohol consumption behavior        |                                   |                                  |                                   |                                  |
| Less than daily                     | 4,157 (85.9)                      | 1,789 (86.8)                     | 2,839 (86.3)                      | 1,263 (87.4)                     |
| Daily                               | 680 (14.1)                        | 271 (13.2)                       | 450 (13.7)                        | 182 (12.6)                       |
| Missing                             | 163                               | 41                               | 111                               | 24                               |
| Tobacco use behavior                |                                   |                                  |                                   |                                  |
| Current smoker                      | 791 (16.1)                        | 367 (17.7)                       | 515 (15.4)                        | 221 (15.2)                       |
| Former smoker                       | 1,065 (21.7)                      | 436 (21.0)                       | 676 (20.3)                        | 331 (22.7)                       |
| Never smoker                        | 3,057 (62.2)                      | 1,273 (61.3)                     | 2,145 (64.3)                      | 903 (62.1)                       |
| Missing                             | 87                                | 25                               | 64                                | 14                               |
| Physical activity (MET-h per week)  |                                   |                                  |                                   |                                  |
| Median (Q1-Q3)                      | 14.0 (0.0-40.0)                   | 14.5 (0.0-40.0)                  | 16.0 (0.3-40.0)                   | 14.0 (0.0-36.0)                  |
| Missing                             | 215                               | 83                               | 148                               | 35                               |

(continued on following page)

**TABLE 1.** Distribution of Cohort Characteristics at 2 Years and 4 Years After Diagnosis, No. (%) (continued)

| Characteristic               | T2, 2 Years After Diagnosis       |                                  | T3, 4 Years After Diagnosis       |                                  |
|------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
|                              | Development Cohort<br>(n = 5,000) | Validation Cohort<br>(n = 2,101) | Development Cohort<br>(n = 3,400) | Validation Cohort<br>(n = 1,469) |
| Tumor stage                  |                                   |                                  |                                   |                                  |
| Stage I                      | 2,535 (50.7)                      | 1,042 (49.9)                     | 1,787 (52.6)                      | 761 (52.1)                       |
| Stage II                     | 1,994 (39.9)                      | 838 (40.2)                       | 1,352 (39.8)                      | 557 (38.2)                       |
| Stage III                    | 467 (9.3)                         | 207 (9.9)                        | 258 (7.6)                         | 142 (9.7)                        |
| Missing                      | 4                                 | 14                               | 3                                 | 9                                |
| Tumor subtype                |                                   |                                  |                                   |                                  |
| HR+ HER2+                    | 520 (10.5)                        | 215 (10.3)                       | 358 (10.6)                        | 155 (10.6)                       |
| HR+ HER2–                    | 3,821 (77.0)                      | 1,597 (76.2)                     | 2,607 (77.2)                      | 1,112 (75.9)                     |
| HR– HER2+                    | 201 (4.0)                         | 82 (3.9)                         | 128 (3.8)                         | 63 (4.3)                         |
| HR– HER2–                    | 422 (8.5)                         | 203 (9.7)                        | 284 (8.4)                         | 135 (9.2)                        |
| Missing                      | 36                                | 4                                | 23                                | 4                                |
| Treatment-related factors    |                                   |                                  |                                   |                                  |
| Axillary surgery             |                                   |                                  |                                   |                                  |
| None or sentinel node biopsy | 3,050 (61.0)                      | 1,431 (68.1)                     | 2,128 (62.6)                      | 988 (67.3)                       |
| Dissection                   | 1,950 (39.0)                      | 670 (31.9)                       | 1,272 (37.4)                      | 481 (32.7)                       |
| Breast cancer surgery        |                                   |                                  |                                   |                                  |
| Conservative                 | 3,684 (73.7)                      | 1,572 (74.8)                     | 2,568 (75.5)                      | 1,107 (75.4)                     |
| Mastectomy                   | 1,316 (26.3)                      | 529 (25.2)                       | 832 (24.5)                        | 362 (24.6)                       |
| Chemotherapy                 |                                   |                                  |                                   |                                  |
| No                           | 2,358 (47.2)                      | 999 (47.5)                       | 1,678 (49.4)                      | 694 (47.2)                       |
| Yes                          | 2,642 (52.8)                      | 1,102 (52.5)                     | 1,722 (50.6)                      | 775 (52.8)                       |
| Radiotherapy                 |                                   |                                  |                                   |                                  |
| No                           | 437 (8.7)                         | 132 (6.3)                        | 293 (8.6)                         | 108 (7.4)                        |
| Yes                          | 4,561 (91.3)                      | 1,969 (93.7)                     | 3,106 (91.4)                      | 1,361 (92.6)                     |
| Missing                      | 2                                 | 0                                | 1                                 | 0                                |
| Hormonal therapy             |                                   |                                  |                                   |                                  |
| No                           | 889 (17.8)                        | 361 (17.2)                       | 610 (17.9)                        | 253 (17.2)                       |
| Yes                          | 4,111 (82.2)                      | 1,740 (82.8)                     | 2,789 (82.1)                      | 1,216 (82.8)                     |
| Missing                      | 0                                 | 0                                | 1                                 | 0                                |
| Anti-HER2 therapy            |                                   |                                  |                                   |                                  |
| No                           | 4,429 (88.6)                      | 1,827 (87.0)                     | 3,012 (88.6)                      | 1,265 (86.1)                     |
| Yes                          | 571 (11.4)                        | 274 (13.0)                       | 388 (11.4)                        | 204 (13.9)                       |
| Symptoms                     |                                   |                                  |                                   |                                  |
| Anxiety                      |                                   |                                  |                                   |                                  |
| Noncase                      | 1,865 (39.0)                      | 829 (41.8)                       | 1,289 (39.6)                      | 571 (40.3)                       |
| Doubtful                     | 1,261 (26.4)                      | 515 (26.0)                       | 867 (26.6)                        | 364 (25.7)                       |
| Case                         | 1,654 (34.6)                      | 638 (32.2)                       | 1,101 (33.8)                      | 483 (34.1)                       |
| Missing                      | 220                               | 119                              | 143                               | 51                               |
| Depression                   |                                   |                                  |                                   |                                  |
| Noncase                      | 3,926 (82.0)                      | 1,638 (82.6)                     | 2,716 (83.3)                      | 1,172 (82.5)                     |
| Doubtful                     | 527 (11.0)                        | 220 (11.1)                       | 328 (10.1)                        | 155 (10.9)                       |
| Case                         | 332 (6.9)                         | 125 (6.3)                        | 216 (6.6)                         | 93 (6.5)                         |
| Missing                      | 215                               | 118                              | 140                               | 49                               |

(continued on following page)



**TABLE 1.** Distribution of Cohort Characteristics at 2 Years and 4 Years After Diagnosis, No. (%) (continued)

| Characteristic | T2, 2 Years After Diagnosis       |                                  | T3, 4 Years After Diagnosis       |                                  |
|----------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
|                | Development Cohort<br>(n = 5,000) | Validation Cohort<br>(n = 2,101) | Development Cohort<br>(n = 3,400) | Validation Cohort<br>(n = 1,469) |
| Insomnia       |                                   |                                  |                                   |                                  |
| Mean (SD)      | 42.4 (33.2)                       | 43.3 (33.4)                      | 41.2 (32.7)                       | 43.5 (32.9)                      |
| Missing        | 193                               | 88                               | 121                               | 45                               |
| Pain           |                                   |                                  |                                   |                                  |
| Mean (SD)      | 15.4 (21.2)                       | 15.1 (20.5)                      | 14.9 (21.0)                       | 15.4 (20.8)                      |
| Missing        | 160                               | 82                               | 103                               | 39                               |
| Hot flashes    |                                   |                                  |                                   |                                  |
| No             | 3,441 (71.8)                      | 1,358 (69.4)                     | 2,354 (72.5)                      | 951 (68.2)                       |
| Yes            | 1,354 (28.2)                      | 600 (30.6)                       | 893 (27.5)                        | 443 (31.8)                       |
| Missing        | 205                               | 143                              | 153                               | 75                               |

NOTE. Self-reported physical activity assessed by Global Physical Activity Questionnaire-16; Anxiety and Depression scored according to the Hospital Anxiety and Depression Scale: noncase (score 0-7), doubtful (8-10), and case (11-21); Insomnia and Pain assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; Hot flashes assessed by the Common Terminology Criteria for Adverse Events—CTCAE-v 4.0 (yes = any grade). Approximately 22% and 18% among professionally active women in this cohort had not returned to work 2 and 4 years after diagnosis, respectively.

Abbreviations: BMI, body mass index; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MET-h, metabolic equivalent of task hour; Q, quartile; SD, standard deviation.

of chemotherapy and severe fatigue at year 1 (T1), closest to completion of primary treatment (adjusted odds ratio v no 1.270 [95% CI, 1.099 to 1.466]; Data Supplement), this did not seem to persist in later time-point models. By contrast, hormonal therapy represented a significant correlate of severe global fatigue in development models at T2, approximately 1 year into hormonal therapy, and was confirmed as a significant predictor of fatigue at T3, after a longer course of treatment, approximately 3 years.

Model  $\beta$  coefficients for regression equations are presented in [Tables 2](#) and [3](#). The Data Supplement shows model calibration plots.

### Secondary Outcomes Evaluation: Fatigue Dimensions

Prevalence of severe fatigue dimensions followed similar patterns to that of global fatigue, except for emotional fatigue, which tended to progressively improve ([Fig 1](#)). Consistent with global fatigue, there was a close relationship between reporting severe pretreatment fatigue and concomitant pain at diagnosis with each of the three dimensions, and chemotherapy was retained as a risk factor for all dimensions of fatigue at T1 in the development cohort. Dimension-specific predictors at all time points included higher BMI for physical fatigue and emotional distress for emotional and cognitive fatigue (Data Supplement).

### Sensitivity Analyses

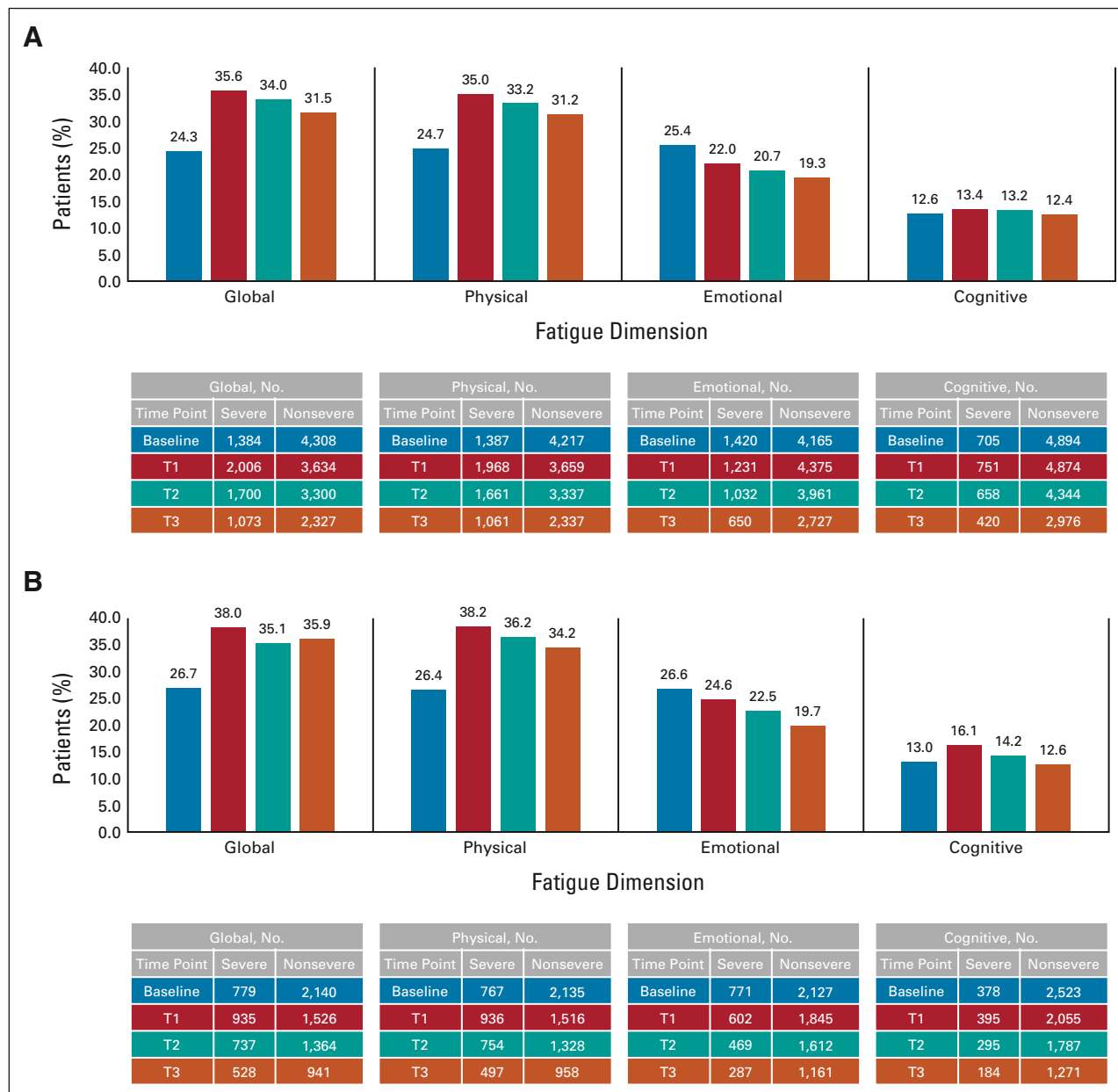
The impact of treatment-related variables on fatigue was consistent in sensitivity analyses. In particular, receipt of

hormonal therapy was a risk factor for longer-term severe fatigue at T3 (data not shown).

## DISCUSSION

Fatigue is a very common side effect among patients with breast cancer, but limited tools exist to predict its risk.<sup>6</sup> About one-in-three patients in CANTO endured persistent, severe fatigue over time. Using the wealth of information of this cohort, we identified clinicobehavioral risk factors and generated a risk model for severe fatigue 2 years after diagnosis of breast cancer, as well as an exploratory model, to provide further insight into risk of severe fatigue 4 years after diagnosis. Dimension-specific risk factors were identified.

Our study confirms and expands the knowledge about relevant risk factors for severe fatigue in survivors of breast cancer.<sup>3,6,11,30-35</sup> Across global and fatigue dimensions, pretreatment fatigue represented the strongest and most consistent predictor. Pretreatment fatigue may set the stage for elevated fatigue even years after treatment completion, because of a disruption in biologic, psychologic, or behavioral mechanisms that exist before treatment onset.<sup>3,4,36-39</sup> Younger age, and, accordingly, premenopausal status, also emerged as risk factors, as previously shown.<sup>5,36,40</sup> In addition, a vulnerable phenotype was represented by patients with high concomitant symptom burden at diagnosis, experiencing several other frequently reported correlates of fatigue, such as sleep disturbances,



**FIG 1.** Prevalence of severe global fatigue and of severe fatigue by dimension over time in (A) development cohort and (B) validation cohort. Baseline represents breast cancer diagnosis.

pain (which may include chronic neuropathic pain further exacerbated by more extensive surgical procedures),<sup>41,42</sup> depression, and anxiety.<sup>3,6</sup> Our results also suggest that several correlates are often shared across distinct fatigue dimensions and over time. However, notable was the closer relationship of physical fatigue with increased BMI and that of emotional and cognitive fatigue with psychologic distress and vulnerability, which highlights a need of examining risk factors in view of their possible dimension-specific effects.<sup>3,6</sup>

There seemed to be variation in the way that treatment-related factors affect fatigue at different stages of survivorship. In the shorter term (T1), we found that the

chemotherapy-related impact seems transitory and mostly evident in the aftermath of treatment, in line with previous reports, for example, those focused on cognitive function.<sup>43,44</sup> By contrast, a more marked detrimental association between hormonal therapy and fatigue was confirmed after longer exposure (T3). From a broader perspective, these findings support the notion that the impact of hormonal therapy on quality of life does not seem to taper off over time. The Mind Body Study had nicely shown that hormonal therapy exacerbates an array of treatment-associated symptoms, being likely responsible for the failure to resolve some common chemotherapy-related toxicities.<sup>45</sup> Analogously, we had previously



**TABLE 2.** Predictive Model of the Risk of Severe Fatigue at 2 Years After Diagnosis

| Variable                                                | OR    | 95% CI         | $\beta$ Coefficient | 95% CI            | P       |
|---------------------------------------------------------|-------|----------------|---------------------|-------------------|---------|
| Severe pretreatment fatigue, <sup>a</sup> yes versus no | 3.191 | 2.704 to 3.767 | 1.160               | 0.995 to 1.326    | < .0001 |
| Age, continuous (for 1-year decrement)                  | 1.015 | 1.009 to 1.022 | -0.015              | -0.021 to -0.0088 | < .0001 |
| BMI, continuous (for unit increment)                    | 1.025 | 1.012 to 1.038 | 0.025               | 0.012 to 0.038    | .0001   |
| Tobacco use behavior, former versus never               | 1.243 | 1.055 to 1.463 | 0.217               | 0.053 to 0.381    | .009    |
| Tobacco use behavior, current versus never              | 1.552 | 1.291 to 1.866 | 0.440               | 0.256 to 0.624    | < .0001 |
| Anxiety, <sup>b</sup> doubtful case versus noncase      | 1.063 | 0.895 to 1.262 | 0.061               | -0.110 to 0.233   | .485    |
| Anxiety, <sup>b</sup> case versus noncase               | 1.265 | 1.073 to 1.492 | 0.235               | 0.070 to 0.400    | .005    |
| Insomnia, <sup>a</sup> continuous (for unit increment)  | 1.005 | 1.003 to 1.007 | 0.0048              | 0.0026 to 0.0070  | < .0001 |
| Pain, <sup>a</sup> continuous (for unit increment)      | 1.014 | 1.010 to 1.017 | 0.014               | 0.010 to 0.017    | < .0001 |
| Intercept                                               |       |                | -1.445              | -1.912 to -0.978  | < .0001 |
| AUC (95% CI)                                            |       |                | 0.73 (0.72 to 0.75) |                   |         |

Abbreviations: AUC, area under the receiver operating characteristic curve; BMI, body mass index; OR, odds ratio.

<sup>a</sup>Scored according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30.<sup>14</sup>

<sup>b</sup>Scored according to the Hospital Anxiety and Depression Scale: noncase (score 0-7), doubtful (8-10), and case (11-21).<sup>23</sup>

suggested how hormonal therapy seems to attenuate the recovery of patient-reported functions that typically get better over time, including emotional function and future perspectives.<sup>7</sup> Data from the present study underscore that some patients receiving hormonal therapy—particularly younger, premenopausal women—may require dedicated attention. This is all the more important in consideration of recently implemented strategies to escalate hormonal therapy by adding ovarian function suppression<sup>46</sup> or extending its duration beyond 5 years.<sup>47-49</sup>

Substantial evidence shows that cancer-related fatigue is underaddressed<sup>3,6,8,50</sup> and that the utilization of strategies to manage this symptom may be suboptimal.<sup>51</sup> In light of the collective research to date, including the present study, we propose a risk-stratified framework of long-term toxicity management, applied to fatigue (Table 4), and an online tool for fatigue risk calculation.<sup>58</sup> We envision a clinical care setting where incoming new

patients are systematically screened for fatigue and risk factors at breast cancer diagnosis, before the initiation of any cancer treatment. Some among them would already experience pretreatment fatigue and require the upfront utilization of interventions to treat this symptom.<sup>8,50</sup> By contrast, among patients without severe fatigue at diagnosis, a detailed evaluation of factors included in our models would allow a more personalized approach.<sup>59-61</sup> The models we propose include several modifiable behavioral risk factors for which meaningful interventions exist as well as concomitant symptom clusters that can be specifically treated, in the context of a comprehensive survivorship care model that addresses multiple dimensions of health and health promotion.<sup>62</sup> In addition, among patients who do not report severe pretreatment fatigue, being at risk of long-term post-treatment fatigue may indicate a more attentive assessment. This can help to increase awareness among providers and patients to

**TABLE 3.** Exploratory Predictive Model of the Risk of Severe Fatigue at 4 Years After Diagnosis

| Variable                                                | OR    | 95% CI         | $\beta$ Coefficient | 95% CI           | P       |
|---------------------------------------------------------|-------|----------------|---------------------|------------------|---------|
| Severe pretreatment fatigue, <sup>a</sup> yes versus no | 2.480 | 2.022 to 3.042 | 0.908               | 0.704 to 1.112   | < .0001 |
| Menopausal status, pre- versus postmenopausal           | 1.325 | 1.123 to 1.563 | 0.281               | 0.116 to 0.446   | .0009   |
| Hormonal therapy, yes versus no                         | 1.448 | 1.165 to 1.799 | 0.370               | 0.153 to 0.587   | .0008   |
| Anxiety, <sup>b</sup> doubtful case versus noncase      | 1.137 | 0.924 to 1.398 | 0.128               | -0.079 to 0.335  | .225    |
| Anxiety, <sup>b</sup> case versus noncase               | 1.460 | 1.196 to 1.781 | 0.378               | 0.179 to 0.577   | .0002   |
| Insomnia, <sup>a</sup> continuous (for unit increment)  | 1.004 | 1.001 to 1.007 | 0.004               | 0.0013 to 0.007  | .003    |
| Pain, <sup>a</sup> continuous (for unit increment)      | 1.016 | 1.012 to 1.021 | 0.016               | 0.012 to 0.020   | < .0001 |
| Intercept                                               |       |                | -2.018              | -2.273 to -1.763 | < .0001 |
| AUC (95% CI)                                            |       |                | 0.71 (0.70 to 0.72) |                  |         |

Abbreviations: AUC, area under the receiver operating characteristic curve; OR, odds ratio.

<sup>a</sup>Scored according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30.<sup>14</sup>

<sup>b</sup>Scored according to the Hospital Anxiety and Depression Scale: noncase (score 0-7), doubtful (8-10), and case (11-21).<sup>23</sup>

**TABLE 4.** Management of Cancer-Related Fatigue Within a Comprehensive Breast Cancer Survivorship Care Framework  
**Interventions to Manage Fatigue and to Address Risk Factors and Concurrent Symptoms of Fatigue**

| For Patients With Fatigue                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | For Patients With Fatigue or High Risk of Developing Fatigue                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Management of fatigue during active treatment<br>Physical activity interventions<br>Initiate exercise programs and/or maintain optimal level of physical activity, combining endurance aerobic and resistance training<br>Rehabilitation: eg, physical therapy<br>Physically based therapies: massage therapy<br>Psychosocial interventions<br>Cognitive behavioral therapy<br>Psychoeducational therapies<br>Mind-body interventions: yoga<br>Nutrition consultation<br>Management of fatigue post-treatment<br>Physical activity interventions<br>Initiate exercise programs and/or maintain optimal level of physical activity, combining endurance aerobic and resistance training<br>Rehabilitation: eg, physical therapy<br>Psychosocial interventions<br>Cognitive behavioral therapy<br>Psychoeducational therapies<br>Supportive expressive therapies<br>Mindfulness-based approaches<br>Mind-body interventions: yoga and acupuncture<br>Nutrition consultation | Correct modifiable risk factors and comorbid factors<br>Reduce excess body weight and obesity<br>Lifestyle interventions for improved energy balance and to pursue weight loss: increase and/or maintain adequate levels of physical activity and/or energy expenditure; Improve nutrition and energy intake<br>Cognitive behavioral therapy<br>Encourage and facilitate smoking cessation<br>Screen for and address concurrent symptoms and treatable contributing factors<br>Emotional distress<br>Cognitive behavioral therapy<br>Mindfulness-based approaches<br>Physical activity<br>Yoga<br>Sleep disturbances<br>Sleep hygiene<br>Cognitive behavioral therapy<br>Mindfulness-based approaches<br>Acupuncture<br>Pain<br>Comprehensive assessment including pain experience, etiology, pathophysiology, and aggravating and alleviating factors<br>Psychosocial support<br>Patient and family and/or caregiver education<br>Nonpharmacologic strategies to be considered on the basis of etiology and pathophysiology: eg, physical and occupational therapy, acupuncture, yoga, and massage<br>Review if concomitant medical causes of fatigue exist and treat them; Consider pharmacologic options to treat symptoms on a case-by-case basis |

**Increase Awareness, Promote Education, and Facilitate Interdisciplinary Referral and Access to Interventions**<sup>8,50,52-57</sup>

|                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Systematically screen and monitor fatigue and its correlates                                                                                                                                         |
| At initial pretreatment visit                                                                                                                                                                        |
| At regular intervals during and after treatment                                                                                                                                                      |
| As clinically indicated                                                                                                                                                                              |
| Using a quantitative or semiquantitative assessment                                                                                                                                                  |
| Improve education and counseling directed to patients and their family and caregivers                                                                                                                |
| Inform about known patterns and risk factors for persistent fatigue                                                                                                                                  |
| Consider management of fatigue as integral part of cancer care                                                                                                                                       |
| Educate to self-monitor changes in fatigue levels over time                                                                                                                                          |
| Encourage to be attentive to symptoms that can herald the onset of persistent fatigue or develop in conjunction with fatigue, including endocrine therapy-related symptoms (eg, menopausal symptoms) |
| Promote self-management skills                                                                                                                                                                       |
| Advise to seek medical help if a persistent deterioration of energy levels exists                                                                                                                    |
| Activate referral network and facilitate access for timely provision of supportive care interventions as appropriate                                                                                 |
| Prioritize interdisciplinary management of fatigue: include physical therapy, psychology, psychiatry, and integrative therapies                                                                      |
| Consider social intervention support for patients who may struggle with lack of resources to obtain access to interventions                                                                          |

recognize symptoms that can herald the onset of persistent fatigue, or develop in conjunction with it, including endocrine therapy-related menopausal symptoms. Increased awareness may then trigger earlier management and referral and facilitate patient access to supportive care when most needed.<sup>50</sup>

Finally, our study offers inspiration for future research in the field, including indications to design meaningful interventional trials. We highlight priorities such as a need to better assess relevant thresholds discriminating between low versus high predicted risk, to validate effectiveness of preventive interventions, to define optimal frequency of

fatigue assessments, and to bridge risk stratification with patient activation toward symptom monitoring and acquisition of self-management skills. Acceptability and interpretability of the model should also be qualitatively explored. Future efforts could also be directed at developing adaptive models that provide a dynamic risk assessment. eHealth might serve well this purpose. Digital tools were used to follow-up patient-reported symptoms, and they were effective in reducing symptom burden and improving health-related quality of life, particularly during or shortly after treatment.<sup>63-67</sup> Nevertheless, although eHealth may potentially facilitate the sustainability of long-term cancer survivorship care, fully automated behavioral intervention technologies for symptom monitoring, real-time feedback, and personalized overview of supportive care options have not consistently improved knowledge, skills, and confidence for self-management among cancer survivors.<sup>68</sup>

The translation of risk prediction into delivery of innovation also comes with several challenges. Model use should integrate clinical judgment to aid decision process, and considerations should be given to issues related to risk communication and incorporation into existing workflows. Social determinants of health should be identified as they may generate disparities in access to interventions and resource utilization, elevating barriers among strata with lower level of health and digital literacy and reduced activation.<sup>69</sup> Notably, 22% and 18% among professionally active women in this cohort had not returned to work 2 and 4 years after diagnosis, respectively, consistent with previous findings.<sup>70,71</sup> The subsequent potential impact on the ability to meet more intense financial demands and on the resources to deal with survivorship-related struggles calls for a need of integrating a social intervention plan into survivorship care models.

Some limitations must be acknowledged. Our models were specifically developed and validated to fit CANTO data and might not be fully generalizable to all cancer populations. CANTO was designed to assess evolution of chronic toxicities among survivors without evidence of active disease, which might influence the trajectory of symptoms. We acknowledge potential for bias because of study termination for patients who experience disease recurrence. Furthermore, patients not providing fatigue assessments at later time points may partly overlap with those at risk of

developing severe fatigue (ie, prone to unhealthy behaviors, with lower income, more symptomatic at diagnosis). Reduced retention may further limit generalizability, and therefore, exploratory models at T3 are provided with the caveat of interpreting their outputs with caution.

Strengths include a large cohort size, a prospective and longitudinal design following patients from diagnosis into treatment completion through the long-term survivorship, and evaluation of distinct, nuanced dimensions of fatigue. Models were internally and externally validated, demonstrating transportability and accurate predictions among patients drawn from a different, although related population.<sup>29,72-74</sup> Performance was globally satisfactory,<sup>60,61</sup> and models performed similarly well when validated in external patients, providing acceptable discrimination (AUC = 0.70-0.80).<sup>75</sup> Consistency with previous literature and plausibility of the underlying risk mechanisms and processes suggest that our models are clinically sound rather than solely relying on statistical selection methods. In addition, our models allow identification of modifiable risk factors and treatable correlate symptoms, and this was suggested to be a key feature to prioritize rather than simply pursuing maximization of model precision.<sup>26,76</sup>

In conclusion, we assessed the long-term prevalence and risk factors for severe fatigue up to four years after breast cancer diagnosis. We then propose predictive models that may help clinicians to better assess fatigue at diagnosis and provide timely management interventions to those experiencing severe pretreatment fatigue. Our models may also aid the prompt identification of modifiable risk factors and raise awareness to recognize early signs and worsening symptoms in patients at long-term risk of severe post-treatment fatigue. This framework may be extended to other prevalent toxicities in survivorship care, building on the integration of patient-reported outcomes in clinical practice and the increasing accessibility to digital symptom management solutions.

Better understanding of mechanisms of fatigue, including its underlying biologic underpinnings, and testing of screening and prevention algorithms in clinical care settings are needed to implement efficient risk-stratified management interventions for cancer-related fatigue.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Development and Validation of a Predictive Model of Severe Fatigue After Breast Cancer Diagnosis: Toward a Personalized Framework in Survivorship Care**

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