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Well-being trajectories in breast cancer and their predictors: A machine-learning approach

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Abstract

Objective: This study aimed to describe distinct trajectories of anxiety/depression symptoms and overall health status/quality of life over a period of 18 months following a breast cancer diagnosis, and identify the medical, socio-demographic, lifestyle, and psychological factors that predict these trajectories.

Methods: 474 females (mean age = 55.79 years) were enrolled in the first weeks after surgery or biopsy. Data from seven assessment points over 18 months, at 3-month intervals, were used. The two outcomes were assessed at all points.

Potential predictors were assessed at baseline and the first follow-up. Machine-Learning techniques were used to detect latent patterns of change and identify the most important predictors.

Results: Five trajectories were identified for each outcome: stably high, high with fluctuations, recovery, deteriorating/delayed response, and stably poor well-being (chronic distress). Psychological factors (i.e., negative affect, coping, sense of control, social support), age, and a few medical variables (e.g., symptoms, immune-related inflammation) predicted patients' participation in the delayed response and the chronic distress trajectories versus all other trajectories.

Conclusions: There is a strong possibility that resilience does not always reflect a stable response pattern, as there might be some interim fluctuations. The use of machine-learning techniques provides a unique opportunity for the identification of illness trajectories and a shortlist of major bio/behavioral predictors. This will facilitate the development of early interventions to prevent a significant deterioration in patient well-being.

KEYWORDS
breast cancer, cancer, oncology, trajectories, trajectory predictors

1 | BACKGROUND

The most common form and leading cause of death due to cancer in adult women is breast cancer (https://gco.iarc.fr/; accessed 24 July 2023). Although the prognosis is typically good, most women will respond to diagnosis and treatment by experiencing variable degrees of distress. This may lead to negative psychological responses, such as fear, hopelessness, or depression.[1] For most patients, psychological health and functioning seem to improve with time.[2] Still, for several others these difficulties may persist for years.[3]

Adaptation to critical conditions is a dynamic process which is not similar for all individuals. Bonanno[4] suggested that adaptation may take the form of four distinct trajectories across time. These patterns include a stably good adjustment trajectory (resilience); a stably poor adjustment trajectory (chronic distress); a trajectory of initially poor but gradually improving adjustment (recovery), and an initially good but deteriorating over time adjustment trajectory (delayed response).

Adaptation to physical illness is also a dynamic process which depends on many factors.[5,6] Regarding breast cancer, research has shown that patients' well-being changes with time, but this change is not similar for all. Helgeson et al.[2] examined mental functioning in 287 patients, seven times over a period of 4 years after surgery, and identified four trajectories. In accordance with Bonanno,[4] most patients (>40%) reported low distress over time; some patients (12%) reported a deterioration over time; one-fourth of the patients showed improvement, and almost one-fifth showed ups and downs with a tendency for improvement. Since then, a growing number of studies has examined the psychological distress trajectories in breast cancer.[7–10] Irrespective of the particular outcome (e.g., distress in general, specific symptoms), almost all studies reported four trajectories of change which were resembling Bonanno's[4] ones. Fewer studies have focused on patients' health status or quality of life. Helgeson et al.[2] identified four trajectories similar to those reported for psychological distress. Other studies[11–13] identified three to four trajectories of physical quality of life or specific difficulties (e.g., fatigue). As most studies have focused on a single aspect of well-being (i.e., either psychological or health status/quality of life-related), it is difficult to ascertain if the trajectories are similar across different aspects of adaptation in the same sample.

Most of these studies have also examined the factors that may differentiate trajectories/groups of patients. Typically, only a few major medical, socio-demographic, or psychological variables were included in each study as differentiating factors. The most frequently reported socio-demographic differentiating factors were age and education.[2,7,8] Also, several psychological variables were identified as differentiating factors, including optimism,[2,9,11] sense of control or self-efficacy,[2,8,11] social support,[2] and (maladaptive) coping reactions.[9,11] The medical factors include physical symptoms, treatment, and cancer stage.[2,8,9,11,13] Younger age, fewer years of education, lower levels of optimism or sense of control and social support, maladaptive coping reactions (e.g., helplessness), more perceived symptoms, and chemotherapy have been associated with worse adaptation to breast cancer. It is important to note, however, that to the best of our knowledge no study has ever simultaneously examined a comprehensive list of medical and disease-related, psychological, socio-demographic, and lifestyle variables so as to identify their potential role as trajectory predictors.

The aim of this study was to extend previous relevant research (a) by addressing a major limitation, that is the focus on rather few predictors of the well-being trajectories, and (b) by examining the potential trajectories of two indices of adjustment/well-being, a psychological and an overall health-related one. Thus, our goal was two-fold. First, to identify distinct trajectories of patient psychological symptoms and overall health status/quality of life over a period

of 18 months following a breast cancer diagnosis in female patients. Second, to identify the factors that may predict these trajectories from a large pool of potential predictors. To achieve these goals, the study employed a novel and vigorous analytic plan based on Machine-Learning (ML) techniques which are well-suited for large amounts of data with complex interactions. The Random Forest (RF), in particular, is considered one of the best-performing ML algorithms as it can handle combinations of categorical and continuous variables, is non-parametric in nature, and is more suitable for high-dimensional skewed data ([14,15]; for further discussion, see Supplementary File 1, Section 1). This is the first study to use ML for the identification of trajectories of patient well-being and their predictors in breast cancer patients.

Four sets of potential predictors were examined: general medical/health and specific disease-related (e.g., stage of cancer, treatment, felt symptoms, etc.); socio-demographic (e.g., age, education); lifestyle (e.g., exercise), and psychological factors. Five domains of psychological factors were assessed all of which have been related to adaptation to breast cancer[16–20]: (I) personality characteristics (i.e., generalized optimism, sense of coherence, resilience-as-trait, and dispositional mindfulness), (II) coping with illness and trauma, and post traumatic growth, (III) perceived social and family support, (IV) perceptions about cancer and related challenges (i.e., self-efficacy to cope with cancer; fear of recurrence) and, (V) emotions and emotional regulation. Two well-established psychological models, which are relevant for adaptation to illness and consider a broader socio-cognitive theoretical context, guided the selection of these five domains: the stress and coping theory,[21] and the Common-Sense Model[5,6] (a detailed discussion of the association between these two models are presented in Leventhal et al.[5]). These theories emphasize personal appraisals/perceptions (domain IV, in this study), coping reactions (domain II, in this study), emotions (domain V), and other personal and social resources, like personality or social support (domains I and III), as significant determinants of adaptation.

Based on theory and previous research, we expected to identify several different trajectories of psychological symptoms and health status. The question was whether the use of ML techniques would reveal the same number and/or form of trajectories as suggested by Bonanno[4] and identified in previous studies, or not. Furthermore, we expected that several medical and psychosocial factors would predict these trajectories. The use of an inclusive list of biological, psychological, and sociodemographic potential predictors and of an analytic plan based on ML may affirm the significance of already known factors (e.g., age, cancer stage, optimism, coping) as predictors of patient well-being or point out new ones.

2 | METHOD

2.1 | Participants and procedure

Data from the BOUNCE Project (https://www.bounce-project.eu/), a study conducted in four countries (Finland, Israel, Italy, and Portugal), was used. Participants were enrolled 2–5 weeks after surgery or biopsy. Inclusion and exclusion criteria are presented in Supplementary File 1. The hospital medical records were used to identify eligible participants and as a source of medical data. The entire study was approved by the ethical committees of the European Institute of Oncology (Approval No R868/18-IEO916) and each participating hospital. A written informed consent was obtained by all participants.

Data from seven assessment points, at 3-month intervals from baseline (M0) to the 18-month follow-up (M18), were used. Psychological symptoms and subjective health status were assessed at all assessment points. Socio-demographic and lifestyle factors were assessed at M0. Medical/disease-related and psychological factors were assessed at M0 or month 3 (M3).

From a total of 706 participants who provided data at baseline (75%–78% of eligible patients agreed to participate), complete data were available for 474 women (a report on missing data is included in Supplementary File 1, Sections 4-5). Participants with complete data at M18 were more likely to be older, employed, and treated with lumpectomy, chemotherapy, or radiotherapy ($p < 0.01$). Participants' characteristics are presented in Table 1.

2.2 | Measures

2.2.1 | Outcome variables

The Hospital Anxiety and Depression Scale (HADS)[22] was used to assess psychological symptoms (14 items; Cronbach's $a = 0.88–0.90$, across assessment points). The Global Health Status scale from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire[23] was used to assess patient subjective health status/overall quality of life (2 items; How would you rate your… overall health during the past week; …overall quality of life during the past week; $a = 0.86–0.88$, across assessment points).

2.2.2 | Socio-demographic variables

The sociodemographic variables included in the study were the country of habitation, age, education level, relational status, employment, income, and existence of significant life stressors (other than disease related) during the first 3 months post diagnosis (see Supplementary File 1 for details).

2.2.3 | Life-style

Smoking history, alcohol consumption, diet, and physical exercise were assessed at baseline (see Supplementary File 1 for details).

2.2.4 | Medical/health and disease-related variables

The medical variables included in the analyses included cancer stage and grade, tumor molecular profile, type of treatment, performance

TABLE 1 Participant sociodemographic and disease-related characteristics ($N = 474$).

Country of habitation/ethnicity	
Israel	106 (22.4%)
Italy	69 (14.6%)
Finland	193 (40.6%)
Portugal	106 (22.4%)
Age	
Mean = 55.79 years; SD = 8.13	
Family status	
Married/living with partner	403 (85%)
Single/widowed	71 (15%)
Education level	
9 years or less	31 (6.5%)
High school	182 (38.4%)
Higher education degree/vocational diploma	261 (55.1%)
Income	
Average or high	371 (79.1%)
Low/very low	99 (20.9%)
Employment	
Employed	339 (71.5%)
Unemployed/housewife/retired	135 (28.5%)
Baseline cancer stage	
Stage I	228 (48%)
Stage II	201 (42.5%)
Stage III	45 (9.5%)
Baseline cancer grade	
Grade I	86 (18.1%)
Grade II	237 (50%)
Grade III	151 (31.9%)
Treatment	
Lumpectomy	354 (74.7%)
Mastectomy	120 (25.3%)
Chemotherapy	249 (52.5%)
Radiotherapy	380 (80.2%)
Endocrine therapy	400 (84.4%)
Anti-HER2 therapy	84 (17.7%)

status, medical history and others (see Supplementary File 1 for details). Patients' functioning status and felt symptoms (e.g., arm symptoms, side effects) were assessed with the relevant scales of the EORTC QLQ-C30 questionnaire[23] and the EORTC Breast Cancer Module[24] (a>0.68 for all scales).

2.2.5 | Psychological variables

Regarding personality factors, dispositional optimism was assessed with the Life Orientation Test–Revised[25] (10 items; Cronbach $a = 0.72$); sense of coherence was assessed with the of the Sense of Coherence Scale[26] (three subscales: meaningfulness, comprehensibility, manageability; 13 items; $a = 0.62$–0.70); trait resilience with the Connor Davidson Resilience Scale[27] (10 items; $a = 0.91$); mindfulness with the Mindful Attention Awareness Scale[28] (15 items; $a = 0.86$). Coping responses were assessed with the Mini–Mental Adjustment to Cancer Scale[29] (29 items assessing helplessness-hopelessness, anxious preoccupation, cognitive avoidance, fighting spirit, and fatalism at M3; fatalism was not included in the analyses due to a very low Cronbach a; a for all other dimensions = 0.60–0.87). The Perceived Ability to Cope with Trauma scale[30] was used to assess the relevant ability (20 items; $a = 0.76$–0.90). Post-traumatic growth was assessed at M3 with the Post-Traumatic Growth Inventory–Short Form[31] (10 items; $a = 0.90$). Social support was measured at M3 with the Medical Outcomes Study Social Support Survey[32] (8 items; $a = 0.91$) and two subscales from the Family Resilience Questionnaire[33] (i.e., communication and cohesion, perceived family coping; 12 items; $a = 0.87$–0.92). Breast-cancer related perceptions were assessed with the Cancer Behavior Inventory[34] (12 items assessing coping self-efficacy; $a = 0.89$), and the Fear of Recurrence Scale-Short Form[35] (9 items; $a = 0.88$). Positive and negative affect were assessed with the 20-item version of the Positive and Negative Affectivity Schedule[36] (20 items; a>0.70, for both subscales). Emotion regulation was assessed with the overall positive and overall negative regulation scores from the Cognitive Emotion Regulation Questionnaire[37] (18 items; $a = 0.70$–0.81).

2.3 | Analyses

Trajectory-based clustering was performed through a novel ML-based clustering approach, utilizing a modified version of the k-means algorithms with the kmlShape package in R. This method was preferred over more traditional methods, such as Latent Class Analysis, since it is a non-parametric approach and makes no assumption about data distribution.[15] Details on data preprocessing, trajectory-based clustering, and the selection of the optimal number of clusters are provided in Supplementary File 1.

Once the optimal number of trajectory-clusters was determined, both multi-class and binary classification models were developed in order to identify the predictors of patterns of change in well-being. For the binary classification problem, the trajectory-clusters were grouped into two major classes representing the 'good' (e.g., stable good or improving levels of well-being) and 'poor' (e.g., stable low or deteriorating levels) progression outcomes. As such, predictive models were then built to discriminate between these two major trajectory classes. Psychological symptoms and health status were included in the analyses as potential predictors of each other.

3 | RESULTS

3.1 | Identifying distinct trajectories

Inspection of the WSS (Within Sum of Squares) plots suggested an optimal number of up to seven trajectories for psychological symptoms, and up to six for subjective health status (see Supplementary File 2, Figure S2.1). Solutions with more than five clusters included one or two very small clusters (i.e., <5% patients) and at least two clusters representing very similar time courses. Therefore, we opted for the five cluster/trajectory solutions for both outcomes (Figure 1).

Regarding psychological symptoms, the majority of patients displayed either a stable course of few symptoms (no distress trajectory; 24.05% of patients) or relatively few symptoms with a slight increase at M6 (unstable low distress; 32.70%). Several patients initially displayed relatively high levels of symptoms which declined after M3 (recovery; 20.88%). The smallest groups included patients who demonstrated a notable rise in symptom severity primarily after M6 (delayed response; 11.82%), and patients who maintained high levels of symptoms over time (chronic distress; 10.55%).

Regarding subjective health, many patients displayed stable high levels over time (good health status; 18.22%), or generally good health across time with only a temporary decline at M6 (unstable good health status; 26.27%). Several patients displayed improving (recovery; 21.40%), or deteriorating health after M3 (delayed response; 21.40%). The smallest group included patients who reported poor health throughout the study period (chronic distress; 12.71%).

3.2 | Predictors of well-being progression

3.2.1 | Psychological symptom trajectories

The performance of the multiclass classification model was not optimal (see Supplementary File 1). Thus, the comparison was made between patients in the delayed response and chronic distress

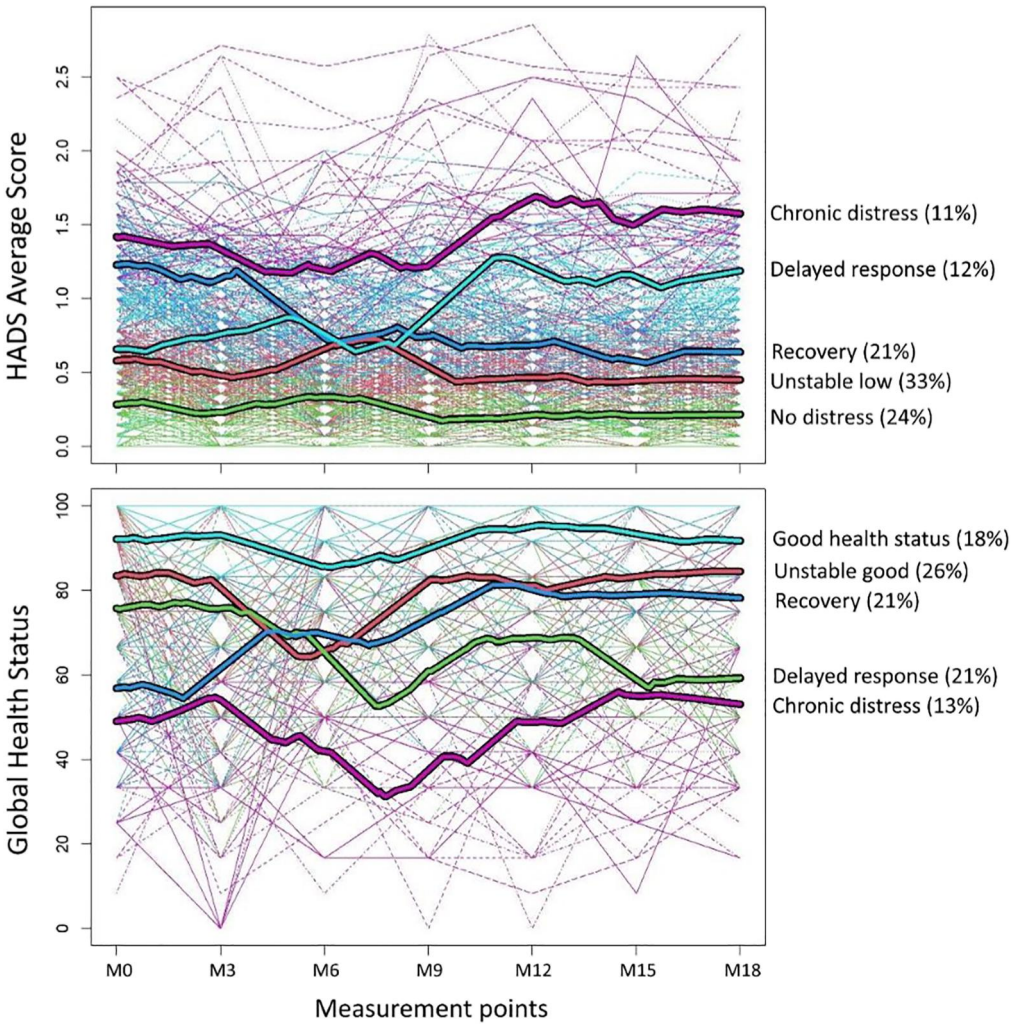

FIGURE 1 Trajectory patterns for psychological symptoms (upper panel) and subjective health status (lower panel). Thin lines represent individual patient trajectories. Bold lines represent the average trajectory for each cluster. HADS, Hospital Anxiety and Depression Scale; M, month. Percentages were rounded to the nearest integer.

trajectories (22.37% of patients) versus patients in all other trajectories (77.63%). The binary classification model displayed very good overall performance (AUC = 0.81, balanced accuracy = 74%, Sensitivity = 77%, Specificity = 72%, Brier Score = 0.21, F^1 = 0.55; see Supplementary File 2, Figure S2.2). The most important predictor variables are listed in Figure 2. 'Variable importance' refers to the degree that a RF model relies on a given variable to make accurate predictions as indexed by the relative influence of each variable to the overall model performance (ranging from 100 to 0, indicating maximum and null contribution to model predictions, respectively).

The list of top-ranking predictors (relative variable importance >40) included positive and negative affect, coping reactions (anxious preoccupation, helplessness, post-traumatic growth), coping self-efficacy, personality characteristics reflecting a sense of control (optimism, coherence–manageability, trait resilience, mindfulness), and overall social support. Moreover, M3 perceived arm symptoms, M0 and M3 overall health status, and age were important predictors of the trajectories. The three most important predictors were M3 negative affect, anxious preoccupation, and arm symptoms.

3.2.2 | Subjective health status trajectories

The comparison was again between patients in the delayed response and the chronic distress trajectories (34% of patients) versus patients in all other trajectories (66%), as the performance of the multiclass classification model was not optimal (see Supplementary File 1). The binary classification model displayed a very good overall performance (AUC = 0.71, balanced accuracy = 65%, Sensitivity = 63%, Specificity = 68%, Brier Score = 0.35, F^1 = 0.51; see Supplementary File 2, Figure S2.3). As displayed in Figure 2, the top-ranking predictors (relative variable importance >40) were coping self-efficacy, M3 psychological distress (anxiety and depression, as assessed by HADS, and negative affect), two types of coping reaction (anxious preoccupation, post-traumatic growth), personality characteristics reflecting a sense of control (coherence–manageability and meaningfulness, mindfulness), and social support-related factors (family communication, total social support). Furthermore, the percentage of neutrophils (the first innate immune responders to injury and inflammation; they are involved in cancer initiation and progression and promote tissue injury-induced inflammation) and thrombocyte count (a component of the blood which reacts to bleeding by initiating a blood clot), perceived side effects, days of sick leave, and BMI emerged as important predictors. The three most important predictors were coping self-efficacy, M3 depression symptoms, and BMI.

4 | DISCUSSION

The study extends previous research on the trajectories of well-being change over time in breast cancer by adopting a novel ML analytic plan, examining an inclusive list of bio/psycho/social potential predictors, and focusing on two major well-being outcomes. This may enable us achieve a more accurate understanding of adaptation to breast cancer.

Most previous studies have identified four trajectories of well-being change: resilience, recovery, delayed response, and chronic distress.[2,7,8,12] Our findings demonstrated the existence of these trajectories but also revealed an additional one: the unstable low distress, regarding psychological symptoms, and the unstable good health status, regarding subjective health. Many patients initially reported relatively high levels of well-being but, in contrast to the 'resilience' trajectory, these levels declined about 3 months after diagnosis or surgery (typically when the adjuvant treatment is fully implemented and side-effects occur). However, their level of well-being started to recover approximately 3 months later (i.e., around the end of active treatment). This trajectory profile was also in contrast to the 'delayed response' patients whose initial good well-being never recovered after

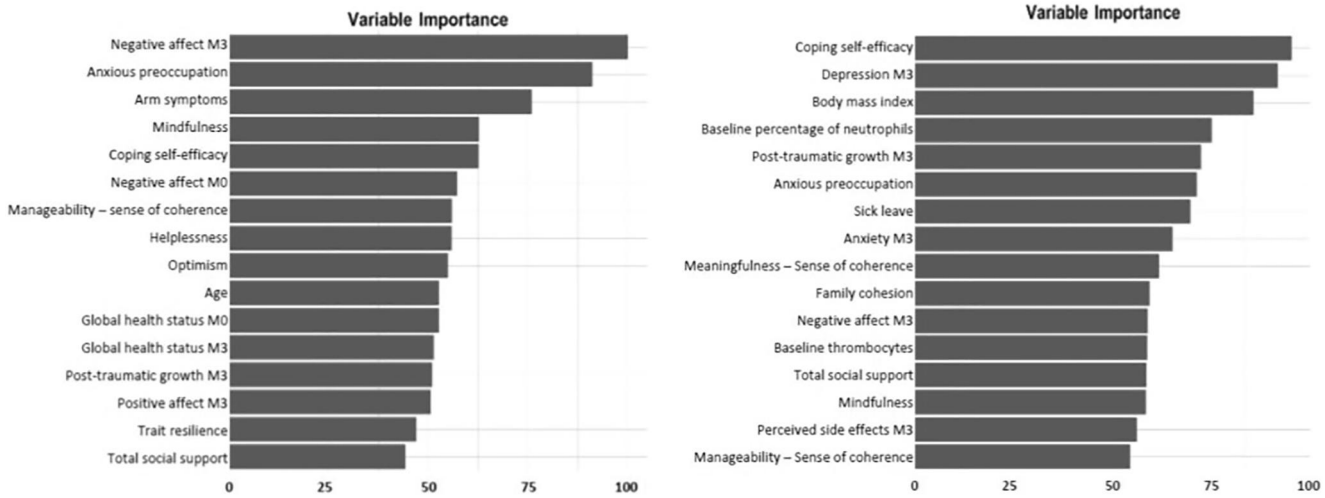

FIGURE 2 The most important predictors (relative variable importance >40) of the psychological symptoms (left panel) and the subjective health (right panel) trajectories (delayed response and chronic distress vs. all other trajectories). M0, baseline; M3, month 3.

a marked deterioration. This raises a question regarding the way that the trajectory of resilience has been defined.

Southwick et al.[38] reached a consensus definition of resilience as a stable trajectory of healthy functioning after a highly adverse event. However, our findings point to the possibility that resilience does not always reflect a stable response pattern. At least regarding breast cancer, there might be some interim fluctuations. Many patients seem to "sway" somewhat in the process of dealing with their illness, but manage to regain their initial well-being levels. Resilience may be manifested by more than one type of trajectory (i.e., one characterized by relative invariance of symptoms throughout recovery), and it is possible that these 'fluctuations' indicate more responsiveness to the disease-related stressful stimuli. Further research is needed to examine this possibility.

The analyses also indicated an informative shortlist of powerful psychological predictors of the well-being trajectories. Namely, negative affect, coping reactions, a sense of control/ability to manage distressing conditions (as reflected in factors like sense of coherence or trait resilience), social support, and self-efficacy to cope with cancer. The importance of these factors has been highlighted by theory[6,21] and previous research.[2,9,11,39] Our findings indicate that the efforts to predict breast cancer patients' adaptation should probably be directed toward these specific factors so as to achieve the best possible outcome.

As in previous research,[2] certain physical symptoms/complaints (e.g., arm symptoms) predicted well-being trajectories. It was surprising that arm symptoms predicted psychological symptoms but not health status. It is possible that such symptoms were a rather expected difficulty and thus did not affect the perception of the current overall health but, still, caused emotional distress. Just a few additional medical/disease-related variables predicted only the health status trajectories. A striking finding was that the type of treatment or cancer stage did not emerge as significant predictors. Moreover, no lifestyle factor predicted the outcomes. Possibly these factors impact well-being indirectly, through other psychological or medical variables. Contrarywise, BMI and two blood-cell count indices related to the immune function (i.e., baseline percentage of neutrophils and thrombocyte count), predicted the subjective health status trajectories. To the best of our knowledge, this is the first time that such specific factors were tested and emerged as predictors of adaptation to cancer. This finding becomes particularly intriguing as it underlines the importance of the biobehavioral interactions for patient adaptation to illness.

Regarding socio-demographics, only age predicted the psychological symptoms trajectories. Education, however, did not predict the trajectories. A possible explanation is that education or other socio-demographic variables (e.g., income) are not directly associated with patient personal experience of illness but, as contextual factors, exert their influence through other factors.

Finally, the findings indicate that psychological symptoms and subjective health status are two closely related variables as they share a similar pattern of trajectories, predict each other, and have certain common predictors. Still, these outcomes are distinct as they are defined by different sets and combinations of predictors (also see[40]).

4.1 | Study limitations

To identify the predictors of the well-being trajectories, the initial patterns were grouped into two major classes due to the relatively low performance of the multiclass classification. Some of the predictors were not assessed at baseline but 3 months later so as to reduce participants' burden or because these factors were likely premature to be assessed at baseline (like coping with the experience of illness). Most participants were rather well-educated and with average or high income, while patients with complete data were more likely to be older and employed, and be treated with chemotherapy or radiotherapy. Hence, it is a question how much the findings generalize to patients with other characteristics. There may be cross-over effects, given that the two outcomes probably affected each other over time. Finally, although the inclusion of a long list of potential predictors is a key strength of the study, it may also lead to chance findings. Thus, although the analyses were conducted very carefully and with the use of a novel analytic plan, a replication of the study is important to verify the findings.

4.2 | Clinical implications and conclusions

The findings indicate that any systematic psychological intervention program should primarily be addressed to those patients who show a delayed or chronic negative response to breast cancer, as they are more likely to have lower well-being in the long run. These interventions should probably take place before the end of the (neo)adjuvant treatment period, as almost no major shifts in the well-being levels were noticed six to 9 months after diagnosis and the beginning of treatment. Additionally, the identification of a few major predictors may help toward the development of applications/interventions that can be used to assist health professionals and patients to better understand patient well-being or even prevent patients' difficulties by targeting these predictors (e.g., coping, illness perceptions, social support). Moreover, the findings highlighted the importance and thus the need for further examination of the impact of certain predictors, like family communication and cohesion, mindfulness, and immune function/inflammation, which are not typically included in relevant studies. Finally, we should stress the usefulness of ML techniques which provided the opportunity to analyze a very diverse and large number of variables. Future studies could also employ these novel techniques so as to achieve a better understanding of complex, multi-dimensional processes, like adaptation to illness.

AUTHOR CONTRIBUTIONS

Evangelos C. Karademas: Conceptualization, formal analysis, data curation, methodology, writing – original draft and review & editing. **Eugenia Mylona**: Formal analysis, software, visualization, writing – original draft. **Ketti Mazzocco**: Conceptualization, funding acquisition, investigation, project administration, writing – review & editing. **Ruth Pat-Horenczyk**: Conceptualization, funding acquisition, investigation,

project administration, writing – review & editing. **Berta Sousa**: Conceptualization, funding acquisition, investigation, project administration, writing – review & editing. **Albino J. Oliveira-Maia**: Conceptualization, funding acquisition, investigation, project administration, writing – review & editing. **Jose Oliveira**: Writing – original draft. **Ilan Roziner**: Conceptualization, data curation, investigation, writing – review & editing. **Georgios Stamatakos**: Funding acquisition, methodology, writing – review & editing. **Fatima Cardoso**: investigation. **Haridimos Kondylakis**: Data curation, resources. **Eleni Kolokotroni**: Data curation, resources. **Konstantina Kourou**: Data curation, formal analysis. **Raquel Lemos**: Investigation. **Isabel Manica**: Investigation. **George Manikis**: Data curation, formal analysis, software. **Chiara Marzorati**: Investigation, methodology. **Johanna Mattson**: Funding acquisition. **Luzia Travado**: Conceptualization, writing – review & editing. **Chariklia Tziraki-Segal**: Conceptualization, funding acquisition, methodology, writing – review & editing. **Dimitris Fotiadis**: Resources, software. **Paula Poikonen-Saksela**: Conceptualization, funding acquisition, investigation, project administration, supervision, writing – review & editing. **Panagiotis Simos**: Conceptualization, data curation, formal analysis, funding acquisition, methodology, supervision, writing – original draft and review & editing.

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CONFLICT OF INTEREST STATEMENT

Albino J. Oliveira-Maia was the national coordinator for Portugal of a non-interventional study (EDMS-ERI-143085581, 4.0) to characterize a Treatment-Resistant Depression Cohort in Europe, sponsored by Janssen-Cilag, Ltd. (2019–2020), and of trials of psilocybin therapy for treatment-resistant depression, sponsored by Compass Pathways, Ltd. (EudraCT number 2017-003288-36) and of esketamine for treatment-resistant depression, sponsored by Janssen-Cilag, Ltd. (EudraCT NUMBER: 2019-002992-33). He is also recipient of a grant from Schuhfried GmBH for norming and validation of cognitive tests. Fatima Cardoso has a consultancy role for Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, Gilead, GlaxoSmithKline, Iqvia, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre- Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seagen, Teva, Touchime. All other authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The anonymized data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

ETHICS STATEMENT

The study has been approved by the ethical committee of the European Institute of Oncology (Approval No R868/18-IEO916) and the ethical committees of each participating hospital, and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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SUPPORTING INFORMATION

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