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BOUNCE

Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back

Research and Innovation Action
SC1-PM-17-2017: *Personalised computer models and in-silico systems for well-being*

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Initial Design and Implementation of the Preliminary *In-Silico* Resilience Trajectory Predictor

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2. Introduction

The current deliverable is mainly focused on the initial design and implementation of the preliminary in-silico resilience trajectory predictor. The BOUNCE trajectory predictor will exploit effectively factors collected during the designed prospective study. This set of factors consists of: (i) patient-reported outcomes (i.e. mental health, distress level, health- and overall Quality of Life (QoL), and functionality), (ii) illness-related self-regulation variables (i.e. self-rated health etc.), (iii) potentially stressful events taking place during the follow up period, (iv) moderators - facilitators (i.e. self-efficacy, resilience, social support etc.) and (v) lifestyle factors (i.e. health habits etc.). Resilience modelling requires building theoretically plausible, clinically useful, and computationally sound schemes describing: (i) the predominant mechanisms involved in the process of psychological adaptation to cancer and (ii) the most powerful longitudinal predictors of long-term psychosocial and functional outcomes following treatment for breast cancer. This goal could be effectively addressed using conventional multivariate statistical methods, such as path analysis, structural equation modelling using latent constructs, logistic regression, and survival statistics, to name the most popular methods. Although, these techniques could be adopted for modelling resilience over time as individual trajectories, they could not predict adaptation to illness as a dynamic process through a composite framework wherein the contribution of each trajectory to the end-point outcomes is assessed and evaluated.

BOUNCE, aspires to go further and develop a prediction tool that can be used at any point during the course of diagnosis and treatment for breast cancer to identify patients at risk for poor psychosocial and functional outcomes--that is patients who, at a given point in time, demonstrate poor psychological resilience. In its final form this tool should have the capacity to identify subgroups of persons defined on individual resilience levels (as a proxy for risk of adverse psychosocial outcome) using a limited number of validated predictors and moderators. The novelty of the BOUNCE computational approach is two-fold. First, it takes full advantage of longitudinal measurements of potential predictors to test models that include both one-time measurements of each predictor (cross-sectional predictor models) as well as individual trajectories of each predictor. Secondly, given the inherent complexity of the longitudinal data, BOUNCE will develop and evaluate a **Machine Learning (ML) framework** to identify subgroups of patients that display distinct psychosocial profiles (at specific time points and over time) in adapting to breast cancer. Importantly, these models will be constantly validated against the aforementioned QoL and functionality end-points.

Along these lines, **four main methodological axes** have been designed based on the available cross-sectional and longitudinal data and according to representative clinical scenarios. Firstly, a cross-sectional clustering methodology is followed aiming at the determination of basic clusters of patients that at a given time point belong to a specific ‘level’ of adaptation to illness. In this approach resilience is defined according to the observation of affective and functional status. Secondly, cross-sectional resilience status prediction is assessed using ML techniques for the formulation of a classification scheme able to identify those medical and psychological/ behavioural factors that are related to and distinguish between the resilience categories having been identified in the first type of analysis. In the third axis of the current methodology, longitudinal data are exploited through a clustering methodology aiming to distinguish patient profiles according to possible transitions from one resilience category to another due to changes in specific factors. Finally, prediction of resilience based on the longitudinal data collected during

the BOUNCE pilot study is performed aiming at the determination of the factors or interactions among them that can more accurately predict final and intermediate outcomes and the resilience level.

Furthermore, **a decision-level fusion model** from all clinical predictive outcomes (probabilistic soft outcomes) has been designed in order to investigate whether the ensemble of the decisions further improves prediction of resilience at a specific time point. ML techniques based on majority voting are employed for building an aggregate model which will improve the classification performance of the single learners utilized in the previous analysis. In addition, an integration methodology of the trajectory predictors will be adopted and implemented to be delivered as software services through the BOUNCE platform. A trajectory analysis with the application of conventional statistical methods to the BOUNCE retrospective data is also presented. All the models developed within the project lifetime will be stored in the Model Repository (see subsection 5.1).

3. Processes involved in psychosocial adaptation to cancer: Analyses of the data from the prospective clinical pilot study

The **Common-Sense Model (CSM) of self-regulation** (Leventhal, H et al. 2005) serves as the basic theoretical model for the formation of prediction models and for the identification of predictors within BOUNCE, since it is the most respected and evaluated relevant theory of the processes and mechanisms of illness self-management (Leventhal, W. et al. 2008). It provides the framework for identifying the processes underlying the initiation and support of behaviours in response to health threats. The CSM model enables the understanding of adherence to treatments and lifestyle changes and can also be used to account for transitions in behavioural patterns during the course of illness (i.e. from adherence to non-adherence and from non-adherence to adherence). Figure 1 depicts the initial cognitive-emotional response after treatment, which can change over time both spontaneously and in response to new stressors including the input from others, such as physicians and family members.

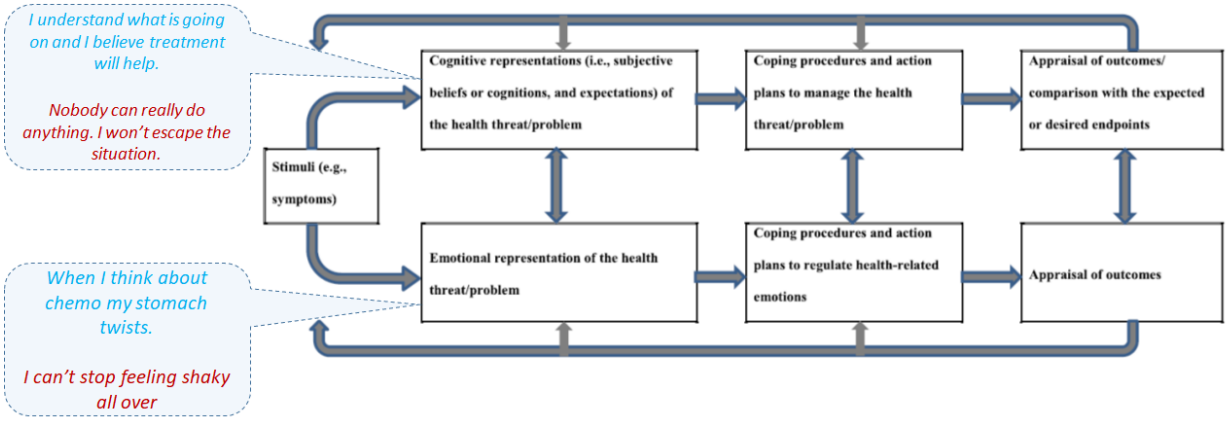

Figure 1. Conceptual model of interacting psychological events involved in illness adaptation according to the Common Sense Model.

Two types of internal (psychological) events are described, namely the cognitive representations of the health threats and the emotional responses, according to the mechanisms underlying well-known predictors of self-management. These in turn, guide coping procedures and action plans which determine outcomes. According to the concept of self-regulation within the CSM, a patient evaluates external (e.g., test results as explained by physicians, other persons'

experiences) and internal (e.g., felt symptoms, personal knowledge and experience, goals and habits) sources of information in relation to several factors (such as family responsibilities etc.) for understanding illness representations. The patient adopts action plans and coping behaviour so as to achieve better adaptation to illness, well-being, and health outcomes. It is worth mentioning that self-regulation for managing illness threats can be moderated by personal and environmental factors (e.g., personality, family, health care system, other stressful events). Therefore, a detailed understanding of illness threats and how they affect the patient's experience, moods, and function is required when dealing with the self-regulation approach (Leventhal, P. et al. 2016).

The concept of resilience has a potentially significant role in self-regulation. According to the ways resilience has been defined in BOUNCE (see deliverables D2.1 and D2.2), and based on the CSM suggestions, resilience-as-trait may be predictive of specific parts of the self-regulation process. **Resilience-as-trait** at time point T1 may predict, for example, (i) a positive representation of illness at T2+ (e.g., illness as a more controllable condition), (ii) a more functional coping behaviours at T3+ (e.g., make plans, adhere to medical advice) and (iii) better outcomes (e.g., fewer psychological symptoms) at Tn. Furthermore, resilience-as-trait may also affect the basic self-regulation mechanism by moderating and/or regulating the associations between the different aspects of this process. For instance, trait resilience may interact with a negative representation (e.g., low level of perceived control over illness) at T1. Although this type of illness representation typically results in dysfunctional coping at T2+ (e.g., avoidance), high levels of resilience may prevent its detrimental impact. In such a case, better outcomes (e.g., fewer psychological symptoms) at Tn are also expected.

Unfortunately, resilience-as-trait measurement is subject to significant drawbacks, for instance people understand themselves in different ways. We could model trait resilience trajectories over time and assess the association between different trajectory shapes to endpoint outcomes. However, instead of looking at resilience through the "eyes" of the patients which is subject to report bias and it is also likely to be affected by illness representations, coping strategies etc., we also look at resilience by modelling the person's affective and behavioural responses to the disease and to subsequent negative events (i.e. stressors) (Figure 2). Hence, the second definition of **resilience-as-process** is inferred from the observation of positive adaptation to illness and better outcomes, despite any negative events such as initial diagnosis, subsequent therapy side-effects, negative test results etc. The outcomes at T1-Tn could be on a single dimension (i.e. QoL and mental health/affective state and functionality) or complementary outcomes considered separately (i.e. QoL, mental health/affective state, functionality and physical health).

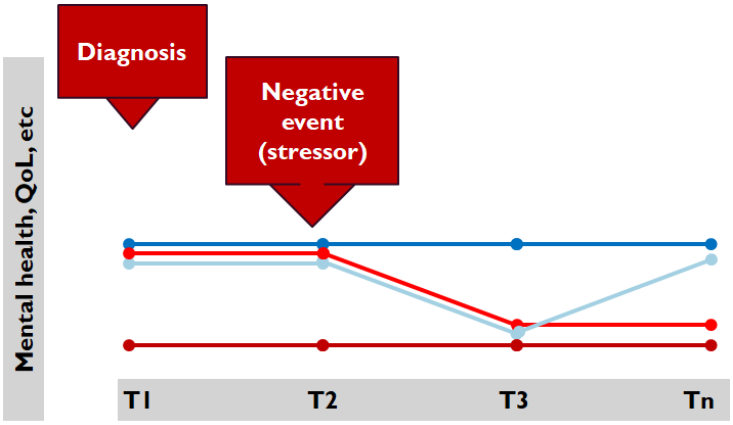

Figure 2. Schematic representation of trajectories of psychosocial and functional illness outcomes during the course of illness. T1 represents measurements at the time of cancer diagnosis. Within BOUNCE Tn represents each subsequent outcome measurements up to 18 months after diagnosis. Each line indicates one patient or subgroup of patients displaying similar adaptation to illness. Additional stressors may emerge at various time points that may affect the adaptation process in varying degrees.

3.1 Identify different types of trajectories at specific time points

The aim of this set of analyses will be to identify subgroups of patients who at a given time point display a specific, distinct 'level' of adaptation to the disease. Given the great diversity of individual responses, as well as the large number of available indicators of the multifaceted process of adaptation and well-being, there is a need to classify patients' degree of adaptation at each time point in different categories (e.g., high adaptation/resilience patients, medium-high, medium-low, poor adaptation/resilience patients). In order to perform this "grouping by adaptation", three types of outcomes will be considered: current mental health and illness-related distress, QoL, and functioning. The combination of these indicators will result to symptom clusters for classifying study participants in different groups/levels of adaptation to illness/resilience at each particular time point. The identification of these categories at different time points will permit the monitoring of patients – whether they stay in the same category across time or change from one to another (i.e., whether their resilience level deteriorates or improves over the progress of illness) and will also enable examining the implicated medical and psychological/behavioural factors. This approach is exemplified in Clinical Scenario I and described in detail in Section 4.1.1 '**Statistical analysis and unsupervised learning**'.

In the simplest framework outlined in Figure 3, the initial diagnosis is treated as the major negative event that mobilizes the adaptation process. Obviously, good and poor outcomes at Tn are observed regardless of prior patient status. The main drawback in this conceptualization is the fact that prior status which is related to the outcome factors is not known and is not taken into account.

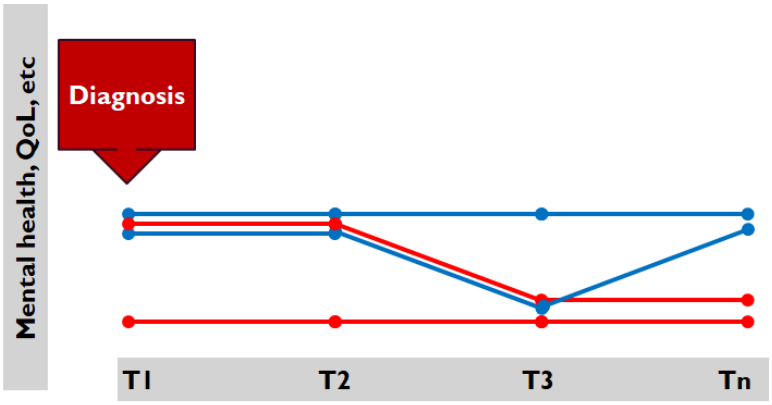

Figure 3. With cancer diagnosis as the principal stressor that mobilizes the adaptation process, two groups of patients are identified according to end-point psychosocial/functional status (poor indicated by red lines and fair indicated by blue lines). Individual differences in trajectory profiles over T1-Tn measurements are not taken into account in this approach. Conventions are the same as in Figure 2.

Clinical scenario I

Patient A at Time X displayed high level of everyday functioning (e.g., performed daily chores with ease, effortlessly planned future activities etc.), good mental health (e.g., low scores in depression and anxiety), and low distress regarding her current and future medical condition. Patient B at the same time point reported a medium level of functioning (e.g., most times, but not always, performed daily chores easily), less than optimal mental health (e.g., medium scores in depression), high distress about her current medical condition but low distress about the progression of illness in the future. Patient C, on the other hand, reported a minimum level of functioning, great depression and anxiety, and high scores of illness-related distress. Finally, patient D at Time X presented a 'mixed' profile: she reported good functioning, but high depression and rather high illness-related distress. Please, note that patients A, B and C had received a positive initial diagnosis, whereas patient D was faced with a less positive initial diagnosis.

When affective and functional status take into account individual variation in intermediate negative events, resilience-as-process is inferred from the observation of positive adaptation to illness and to subsequent negative events (e.g., treatment side-effects, negative test results) as outlined in Figure 4 and exemplified in Clinical Scenario II (outlined in detail in Section 4.1.2 **'Predictive modelling for resilience status')**. Presence of negative event(s) can be considered as a separate variable measured at each time point affecting the outcomes (i.e. mental health, QoL, etc.). The aim of the analyses outlined in this section is to identify those medical and psychological/behavioural factors that are related to and distinguish between the resilience categories. This will provide the opportunity to identify the factors that are more prominent for adaptation to illness at any particular time point. This task is important in three ways: a) estimating individual status on these important factors will permit health professionals to predict patients' short-term adaptation and resilience level and take corrective actions, if needed, to enhance adaptation; b) understanding the factors that are closely related to short-term adaptation and resilience level, and especially those that are amenable to intervention (e.g., social support, illness representations, obesity, tumour level and genotype), will provide health professionals with the opportunity to intervene and enhance short-term adaptation and resilience in a timely fashion; c) the comparison between the factors that are more predictive of short-term adaptation/resilience at different time points will probably permit a more accurate

comprehension of resilience as a process which changes over time and the factors that are related or lead to this change.

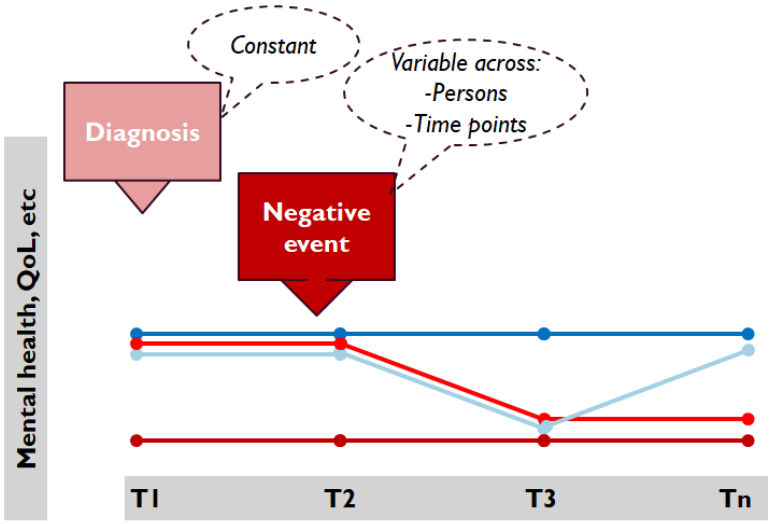

Figure 4. Model that takes into account individual differences in response to stressors occurring after diagnosis. Conventions are the same as in Figure 2.

Clinical scenario II

Patient A (please, see Clinical Scenario I) at Time X also reports high levels of resilience as a typical characteristic of her personality, high levels of optimism, and satisfactory support coming from members of her family. Conversely, patient C (also, see Clinical Scenario I) reports low levels or trait resilience, rather medium levels of optimism, is not satisfied by the amount of social support received, and she perceives her diagnosis and felt symptoms in a negative way (e.g., represents illness as uncontrollable). Patients B and D, both report medium levels of trait resilience, optimism and spirituality. These two patients have received a different initial diagnosis (see clinical scenario I), while patient B also reports higher levels of social support in comparison to patient D. In addition, patients A and D have recently received alarming results from a medical examination. Are all these factors related to patients' current adaptation/resilience level? For example, does optimism or the results from recent medical exams determine primarily patients' current level of resilience reflected in their affective and functional status? Our analyses might provide an answer to this (and many similar) questions.

3.2 Identify different types of resilience trajectories over time

Taking into account longitudinal measurements of patient status (emotional, functional) as well as of potential psychosocial predictor/moderator factors has two key advantages. Firstly, it permits modelling individual differences in changes in patient status over time as exemplified in Clinical Scenario III. Secondly, it allows for modelling of complex interactions between different types of factors in determining the course of patient status.

Clinical scenario III

Although patient A (in Clinical Scenario I) showed very good adaptation and high resilience at time point X, six months later her condition deteriorated. She reported significant difficulties in performing daily chores; she scored high on scales of depression and anxiety and admitted high distress regarding her current and future medical

condition. A few weeks earlier she had received bad news from her scheduled medical exams. Moreover, she reported a sharp decline in the amount of support received by her family. Patient B's status, however, improved. Six months following time point X, she reported really good functioning, better mental health and low illness related distress. In addition, she reported some very good news from her physician and improved levels of proactive behaviours (e.g., she recently engaged in a physical exercise program). Patients C and D did not report any change in their status.

The aim of this type of analysis is to identify patients' potential shifting from one adaptation/resilience category to another due to changes in medical and/or psychological/behavioural factors. This will permit a more accurate estimation of the number of patients who shift from one category to another during the trajectory of illness, the possibility of a patient to shift from high to low resilience and vice versa, as well as the most possible time point after diagnosis for such a change to take place. Furthermore, these analyses will lead to the grouping of the overall process of adaptation to illness and the resilience level into distinct clusters of patients' behaviour (e.g., solid resilience patients, improving resilience, deteriorating resilience, steadily poor resilience etc.). This, in turn, will lead to better understanding of which resilience/adaptation category at different time points is most predictive of the final outcome classes (i.e., adaptation/resilience levels at the final time point). Although some 'flexibility' with regards to the grouping of each patient is expected in the trajectory of illness, the actual degree of shifting between resilience categories is unknown. Thus, this type of analysis will inform health professionals about the possibility of a particular patient's affective and functional status to worsen or improve over time. Even more, these analyses will serve as the basis for the next and more important step. That is, the identification of the factors that determine final outcomes and the overall patient resilience.

In order to fully comprehend the second major advantage of longitudinal modelling, it is important to consider the complexity of illness adaptation as a psychosocial process. Thus, in the context of efficient utilization of cognitive-emotional resources for self-regulation, resilience-as-process may also be inferred from evidence of positive impact of other factors (e.g., optimism, self-efficacy) on the self-regulation process over time. Thus, a good outcome (high resilience) at Tn may relate to low optimism at T1 and conversely low resilience at Tn may be related to high optimism at T1. One of the aims of the set of analyses described in this section, is to model outcomes at each measurement point Tn as a function of (1) the medical and psychological/behavioural factors (or their interactions) assessed at the immediately previous time-point, (2) the factors (or their interactions) assessed at all previous time-points and baseline, as well as (3) the interactions between factors assessed at different time-points. Thus, the aim of this final step is to identify those factors or between-factors-interactions that can more accurately predict final (i.e., at 18 months) and intermediate (i.e., at 6, 12… months) outcomes and adaptation/resilience level. The identification of these factors will lead to the development of the BOUNCE end-product: the prediction tool which will guide future diagnostic and intervention efforts in breast cancer patients' affective and functioning status, and adaptation to illness. These analyses will take into account within-person changes in outcome measures as a function of current and/or preceding levels of potential predictor factors (such as social support, coping strategies, self-efficacy, and representations of illness). A more detailed description of this approach is also subsumed under Section 4.2.1 **'Longitudinal Clustering'**.

3.3 Identify longitudinal predictors of long-term psychosocial/ functional outcomes: Supervised modelling

From the preceding discussion it became evident that adaptation to illness is a complex process shaped by diverse psychosocial, medical and psychological factors (see also Clinical Scenario IV). Modelling these processes is probably the most efficacious way to accurately predict patient psychosocial and functionality outcomes. However, comprehensive and reliable estimation of these factors at multiple time points during the course of cancer treatment is commensurate on the availability of a team of specially trained mental health professionals, which is not the rule in cancer care centres worldwide. In order for resilience estimation and prediction tools to be widely incorporated into routine clinical practice it is important to explore the possibility of establishing profiles of patients at risk for negative long-term mental/physical health outcomes using information readily available to physicians. This information may entail brief emotional status self-report scales (assessing anxiety, distress, and mood) administered at each physician follow-up visit (e.g., at 3-6 month intervals).

To achieve this goal, the prediction tool that is envisioned as the end-product of BOUNCE should rely on a limited number of biomedical factors (e.g., disease characteristics, sociodemographic factors, emotional status self-ratings and possibly also clinically used inflammatory biomarkers (such as CRP), that will emerge (and be validated) as significant predictors of outcomes. Focusing on end-point outcomes instead of trajectories for predicting resilience levels of patients, good and poor outcomes correspond to high and low resilience outcomes at Tn, respectively, regardless of prior status (Figure 5). This approach involves taking into account longitudinal profiles of patients featuring transitions from one distinct adaptation/resilience status to another over time as detailed in Section 4.2 '**A longitudinal computational framework for the analysis of BOUNCE psychosocial and behavioural data**'.

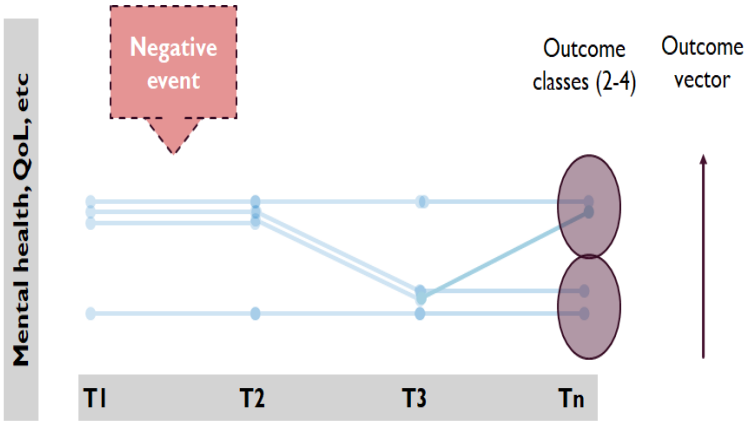

Figure 5. Model to be considered in supervised learning analyses that takes into account individual differences in trajectories of selected outcome measures (emotional status, functionality). Model testing is conducted against patient groupings established on a comprehensive outcome index measured at Tn = 12 or 18 months after diagnosis. Conventions are the same as in Figure 2.

Longitudinal predictors of long-term psychosocial and functional health outcomes will be identified in terms of the longitudinal analysis framework for the analysis of BOUNCE psychosocial and behavioural data described in Section 4.2.2 '**Predictive modelling for longitudinal data**'.

Clinical scenario IV

After 18 months and several ups and down, patient B finally demonstrated good affective and functional status. Patient A, despite the initial success in adapting to the disease, lately reported poor adaptation and very low resilience. Patients' C and D remained stable as in the 9th month after diagnosis. Each patient presented a different profile with respect to their scores on the medical and psychological/behavioural variables included in the study. Significant between- and within-person (i.e., over time) differences were noticed on a range of variables, including social support, coping strategies, self-efficacy, and representations of illness.

3.4 Forthcoming data from the ongoing BOUNCE prospective clinical pilot

The data that will eventually be managed and analysed from the BOUNCE infrastructure include external data sources, retrospective data from the pilot sites, and the prospective data to be available through the pilots. For the external data sources, databases focussing on a) the general population (e.g., data on ageing), b) factors that were not included in BOUNCE (e.g., imaging, assessment of risk factors), or c) factors or conditions not considered by BOUNCE (e.g., social vulnerability in communities, other diseases and health conditions), were excluded from consideration. As such, 14 data sources were examined while only 3 had valuable information that can be reused in BOUNCE. The retrospective data from the clinical sites (IEO, HUJI, and HUS) provide basic clinical information and some of the measurements that have been selected for the prospective study. More details about the external and the retrospective data can be found in the BOUNCE Deliverables D1.3 ('BOUNCE Methodology') and D3.1 ('Identification of Internal and External Data Sources and Registries').

For the prospective data, there will be seven assessment waves, over an 18-month period: baseline, which will occur after the first visit with the oncologist, Month 3 (M3), Month 6 (M6), Month 9 (M9), Month 12 (M12), Month 15 (M15), and Month 18 (M18). During the baseline measurement wave, which will occur within three to four weeks from diagnosis, only non-cancer-specific measures will be delivered (such as personality). Cancer-specific measures will be assessed from M3, when the patient has already had some meaningful experience with the illness.

At baseline and M12 assessments will be collected through Noona during face-to-face encounters with a site researcher (nurse, psychologist, or social worker). During the first face-to-face encounter the researcher will demonstrate the Noona platform and give a short training, so that at the following time points the patient will be able to use Noona independently. More details about the standardized scales and questionnaires to be used in the prospective pilot study can be found in the BOUNCE Deliverable D3.1. Each clinical site (IEO, Rabin Medical Center/Shaare Zedek Medical Center/Kaplan Medical Center [coordinated by HUJI], HUS and CHAMP) is expected to recruit a number of breast cancer patients (660 patients will be recruited altogether from 4 clinical centres).

In order to integrate, homogenize, and semantically uplift the external, retrospective, and prospective data we developed a related ontology and the BOUNCE semantic model. The ontology is used in order to define the mappings, i.e. programmatic correspondences between ontological terms and the various data fields. Based on those mappings, data integration engines automatically homogenize and semantically uplift the available data. More details about the BOUNCE Semantic Model can be found in D3.2 ('Initial Semantic Model').

4. Initial design of Models

The initial design of the models to be developed within WP4 is described in section 4. In the first sub-section, a computational pipeline is presented with the techniques to be applied in the cross-sectional BOUNCE psychological and behavioural data. Statistical and unsupervised methods will be applied aiming at identifying groups of patients which share certain affective/functional status at single time intervals. In addition, a supervised learning framework is described which will be adopted for prediction purposes. In the second sub-section, unsupervised and supervised techniques are described, respectively for the analysis of BOUNCE longitudinal data. Within this computational framework patient profiles across time-points will be established while the factors and their interactions that can accurately predict final and intermediate outcomes will be identified.

4.1 A cross-sectional computational framework for the analysis of BOUNCE psychosocial and behavioural data

4.1.1 Statistical analysis and unsupervised learning

The main scope of this task is to develop an unsupervised learning framework coupled with statistical analysis aiming to identify: a) distinct groups/clusters of patients that share specific affective/functional status at single time intervals (T1, T2, …, TN) during the critical 18-month period following cancer diagnosis, b) the most prominent sociodemographic, clinical and well-being characteristics that differentiate the profile of each cluster from the profiles of all the other clusters together (at a single time interval), and c) grouping/clustering similarities and stability of interpretation to assess cluster-change membership of patients over time points (Dodd MJ et al. 2010). An indicative clinical scenario addressed within BOUNCE unsupervised learning framework is described in **Clinical Scenario I**.

Within BOUNCE cross-sectional analysis, symptom clusters will be generated comprising current mental health and illness-related distress, QoL, and functional level. Discrete levels of each condition will be defined using cut-off thresholds (e.g. high, moderate, mild and low level of each condition) and for validation purposes patients will be labelled according to their corresponding condition (e.g. patient A: high QoL - low illness-related distress - medium level of functioning). Clustering techniques will be used to classify patients based on their symptom clusters (responses to the 3 symptom components) and descriptive statistics and frequency distributions will be calculated to assess quantitatively any differences occurring among the patients' cluster both in terms of their condition and of their clinical, psychosocial, and behavioural characteristics. An illustrative representation of the identified clusters and of how patients are assigned to clusters will be given via clustergrams, radar plots, cluster-change membership, and alluvial diagrams (Figure 6-Figure 8).

<u>BOUNCE cross-sectional unsupervised learning analysis addressing Clinical scenario I</u>

Initially, all patients enrolled in this study including A, B, C, and D will be classified according to the three components of the symptom cluster profile and pre-defined groups/clusters (ground truth labels) will be generated for validating the analysis. Robust and sparse k-means clustering (RSKC) will be applied to the data at each single time interval (Kondo Y. et al. 2016) Due to the high dimensionality and scale of BOUNCE data, RSKC is the clustering model of choice since it assumes that not all factors contribute equally in determining the clusters (different features have varying effects on clustering and noisy features behave in a similar manner across clusters)

and selects the optimal set of features by assigning weights to the features. RSKC will result in an optimal number of features and clusters across the entire examined dataset achieving the highest possible inter- and intra-class cluster similarity. Performance including two major objectives in cluster analysis such as homogeneity and completeness of the clusters will be assessed using several quantitative metrics (e.g., the adjusted mutual information (AMI) score, Fowlkes-Mallows scores, Silhouette coefficient, etc.).

Statistical analysis will be performed relying on the generated clusters, ground truth labels, and medical/psychological/behavioural factors to address specific clinical questions raised by **Clinical Scenario I**.

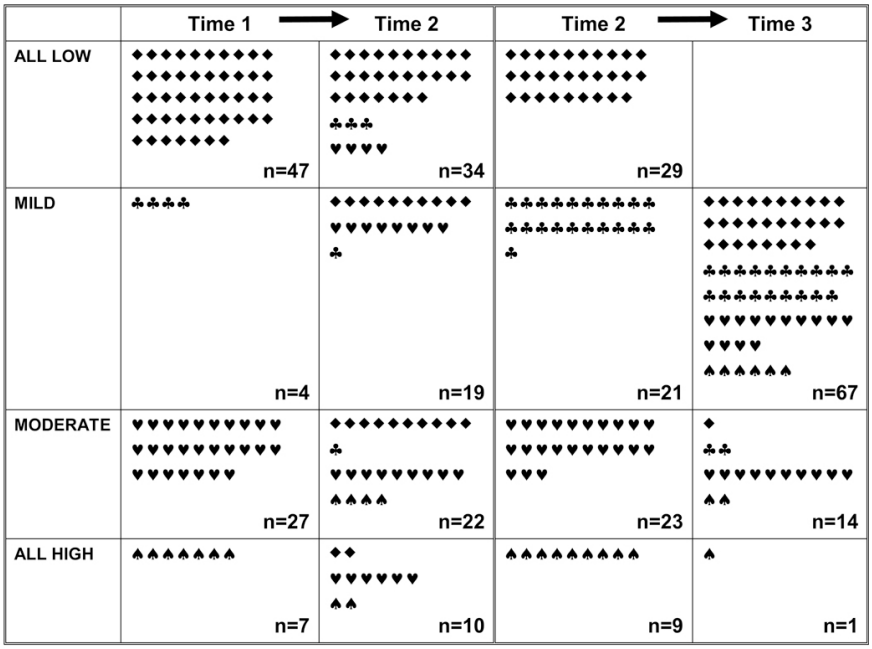

Figure 6. Cluster-change membership of patients across time points 1, 2 and 3. Each symbol type represents low, mild, moderate and high resilience status, respectively. Transitions across clusters are calculated using frequency distributions and descriptive statistics. Image taken from (Dodd MJ et al. 2010).

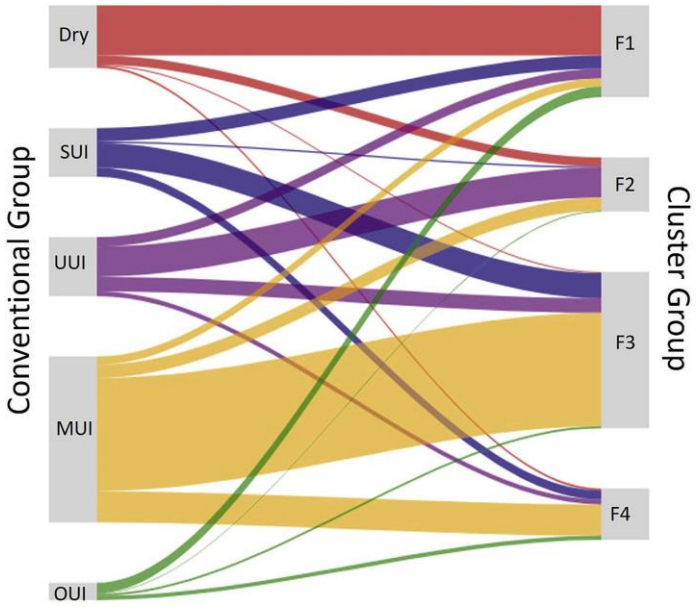

Figure 7. An alluvial diagram of patient group membership depicting deviations in group membership between the ground truth labels generated from patients' profile (left part) and the groups (clusters F1-4) formed using unsupervised sparse k-means clustering. In this type of analysis, the comparison between the actual symptom clusters as defined from BOUNCE data and the generated clusters from sparse k-means clustering will be graphically displayed. Image taken from (Andreev VP et al. 2018).

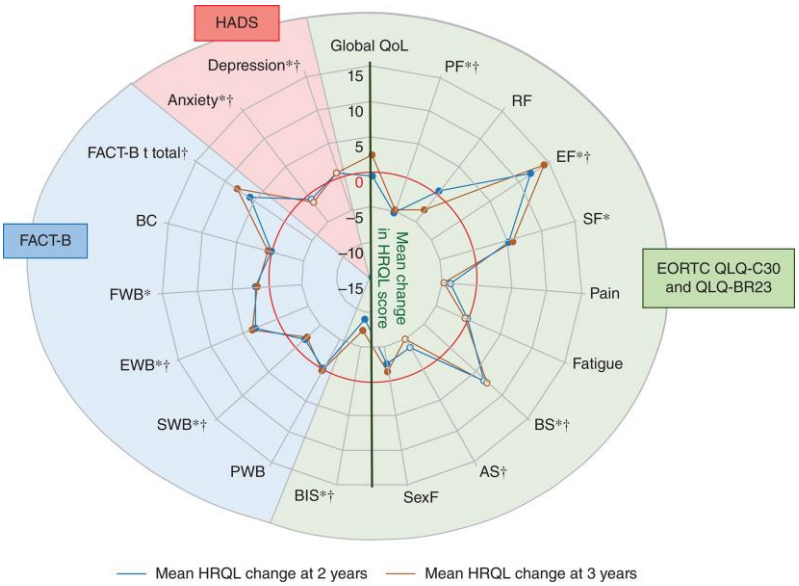

Figure 8. A radar chart showing changes in physical functioning, breast symptoms, body image and psychological distress of women from baseline to the period following breast reconstruction. Image taken from (Winters ZE. et al. 2016). Corresponding radar charts will be reported for each signature of the examined symptom clusters highlighting potential changes in patients' medical, psychological, and behavioural factors.

4.1.2 Predictive modelling of resilience status

This task will develop machine learning-based cross-sectional models to predict end point resilience outcomes at single time intervals (T1, T2, …, TN). The main scope of this analysis is to provide a personalized predictive modelling framework that collects BOUNCE heterogeneous multi-scale data over discrete time points and predicts patient-specific adaptation/resilience status. All models will assign a probability distribution over the examined set of categories (i.e. positive or negative resilience status) at each time interval and a corresponding patient specific graph depicting resilience-as-process will be provided across the examined time points (Figure 9). Feature selection and ranking algorithms will be also applied aiming at identifying those medical, psychological, and behavioural factors that can potentially act as negative events through the follow-up of the studied patients and potentially contribute in discriminating the resilience categories successfully (Figure 10). The proposed predictive analysis framework will be able to address efficiently all clinical scenarios defined within BOUNCE related to prediction of short-term adaptation/resilience at discrete time points (indicative **Clinical Scenario II**).

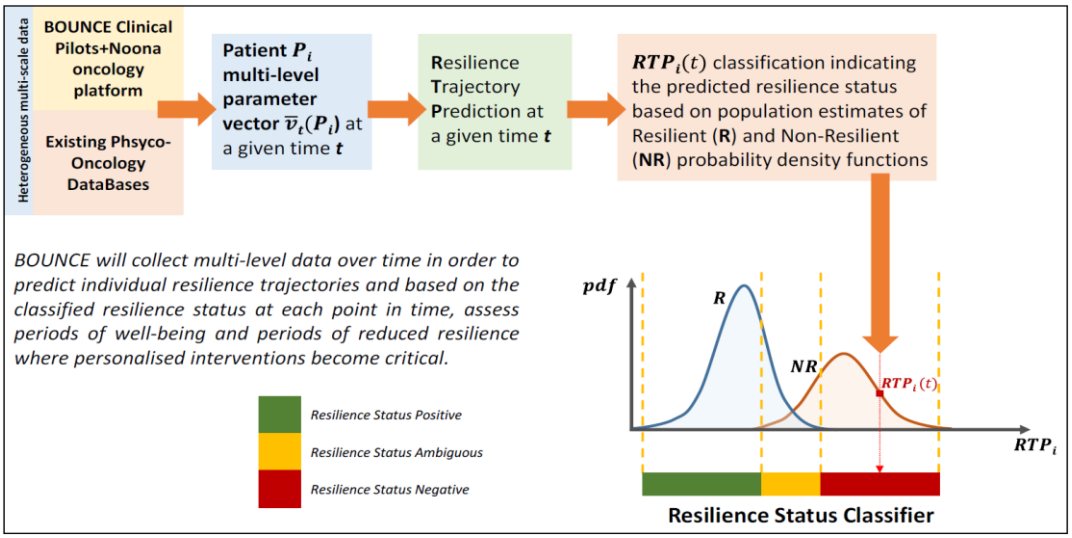

Figure 9. BOUNCE cross-sectional predictive modelling framework for resilience status. Image taken from BOUNCE description of work (DoW).

BOUNCE cross-sectional supervised learning analysis addressing Clinical scenario II

A plethora of predictive models such as eXtreme Gradient Boosting (XGBoost), Generalized Linear Models (GLM), Random Forests (RF), and Weighted Random Support Vector Machine Clusters Analysis (WRSVMC) (Figure 11) will be tested within the BOUNCE supervised learning analysis framework. Selected models have demonstrated good performance with high-dimensional data and incorporate feature ranking/selection techniques during training of the models. A probabilistic outcome will be provided related to resilience status and all medical, psychological, and behavioural factors will be ranked according to their importance in the predictive performance. Feature importance across the examined time intervals will then assist clinicians in recognizing these factors (i.e. negative events) that are more prominent for adaptation to illness at any particular time point of interest along the BOUNCE clinical pilots. To compare all aforementioned models, a large parameter grid will be generated consisting of all models and run in parallel under a nested cross-validation framework (Figure 12) using exactly the same input data during all iterations. The data will be repeatedly split into independent training/testing/validation sets and predictive performance will be quantified in terms of the AUROC and several quantitative metrics including accuracy, sensitivity or recall, specificity, precision, and f1-score where TP, TN, FP, and FN stand for true positive, true negative, false positive and false negative predictions retrieved from the confusion matrix, respectively. Qualitative representation of the classification performance will be demonstrated by the ROC and precision-recall curves and heatmaps (Figure 13).

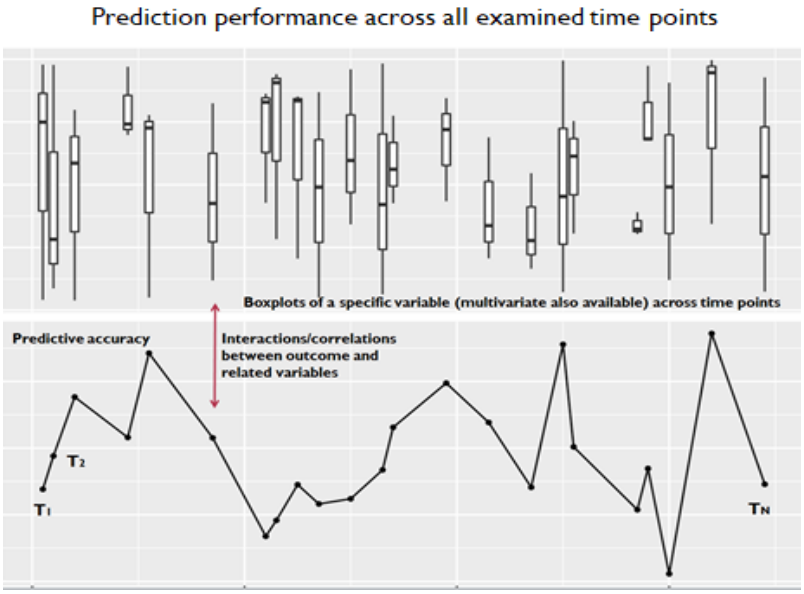

Figure 10. A summary of the predictive analysis results displaying the interaction between a negative event (i.e. important factor that is significant in the predictive analysis) and the predictive performance across the examined time points. Upper panel: the distribution in boxplots of a particular negative event or alternatively grouped boxplots of a particular event with respect to the resilience categories, across time. Lower panel: the predictive accuracy of the model across time. This summary can be also displayed in case of patient-specific negative event - predictive accuracy interactions.

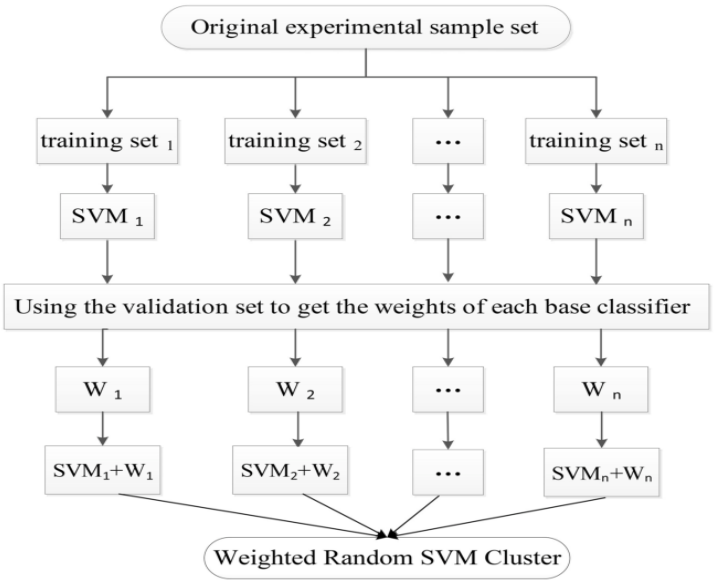

Figure 11. WRSVMC training process. Within BOUNCE, multiple Support Vector Machines (SVMs) will be trained and corresponding weights will be assigned to each single SVM related to their predictive performance. A subset of cases will be selected randomly for training on each iteration, and subsets from all factors will be used to train each single SVM model. The most important factors that contribute to the highest performance of the WRSVMC will be selected as indicative events that best discriminate the resilience categories. Image taken from (Bi XA et al. 2018).

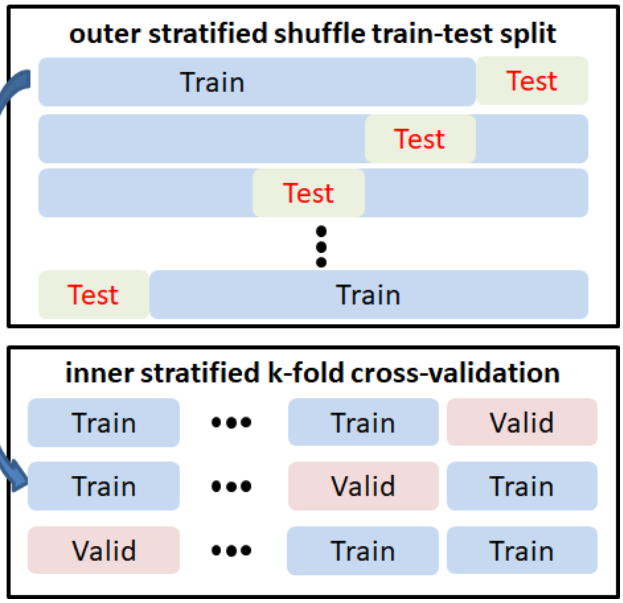

Figure 12. Nested cross-validation process implemented within the BOUNCE analysis framework to assess generalization performance of the examined predictive models and eliminate bias in error estimation.

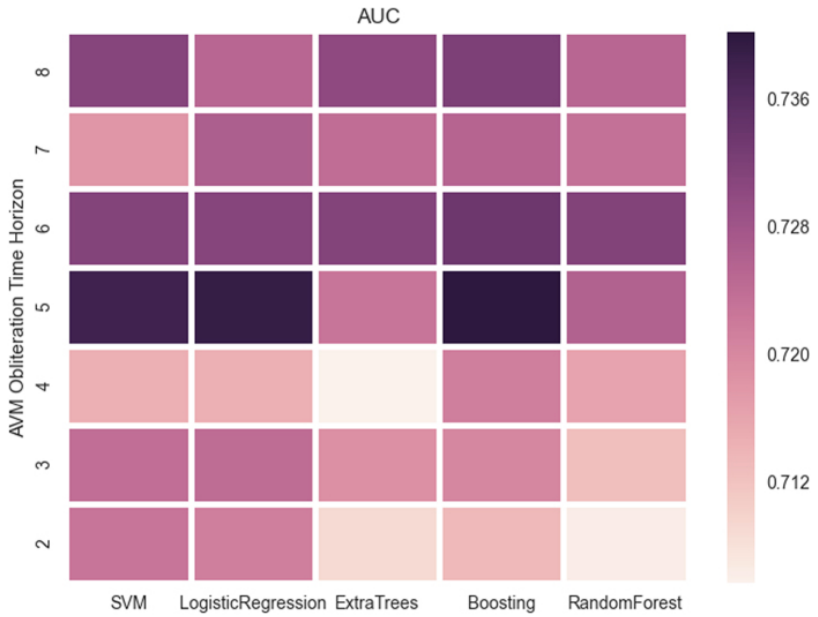

Figure 13. An illustrative comparison of predictive performance for a set of examined predictive models across single time intervals. A heatmap of AUC for the different classifiers depicts the overall performance of each model across the examined time points. Image from (Oermann EK. et al. 2016).

4.2 A longitudinal computational framework for the analysis of BOUNCE psychosocial and behavioural data

4.2.1 Longitudinal Clustering

The aim of this analysis is to establish patient profiles across time-points using unsupervised learning (clustering) techniques. Cluster-change profile of each person over time will be determined revealing the patient's' potential shifting from one adaptation/resilience category to another due to changes in medical and/or psychological and behavioural factors. Within this analysis framework, persons who belong to cluster A at T1, Cluster B at T2 and Cluster A again

at T3 will be grouped together. Determining the shifting from one category to another during the trajectory of the disease will enable the estimation of the exact number of patients that belong to each category. Moreover, an accurate estimation for the possibility of shifting from low to high resilience and vice versa across different time points will be achieved. The overall process of adaptation to illness and the resilience level will be grouped into certain clusters of patients' characteristics and behaviour; thus, empowering the prediction of final outcomes according to the categories that are most informative across time.

This analysis will allow health professionals to estimate the likelihood of a patient's affective and functional status to worsen or improve over time. This type of analysis will serve as the basis for the identification of medical and psychological factors that are more informative for predicting the adaptation to illness and resilience level as a final outcome across the different time points (see below section 4.2.2 for more details).

BOUNCE longitudinal clustering methodology addressing Clinical scenario III

Both machine learning and conventional statistical approaches will be followed to group individual trajectories into distinct clusters and reveal intra-individual changes and inter-individual differences between the examined patients. Latent growth curve modelling (LGCM) and growth mixture modelling (GMM) have frequently been employed to handle data on disease progress of oncological patients after treatment, showing interesting results in trajectory clustering and identifying behavioural risk factors as predictors of trajectory groups (Y. Yang et al. 2018, Bower JE eta l. 2018). Within BOUNCE longitudinal analysis framework, we will employ these methods to identify groups of individuals evolving differently over time and significant factors that may account for the overall process of adaptation to illness and resilience levels that define distinct patient clusters. Trajectory profiles of each cluster will be generated and any medical, psychological, and behavioural factor that is strongly associated with the trajectory profiles will be identified. These methods are further elaborated in sections 6.1 & 6.2. Their application to the retrospective data collected within BOUNCE has provided valuable insights into specific aspects of the process of adaptation to breast cancer as described in detail in sections 6.3-6.6.

A machine learning based resilience clustering approach will be also applied providing distinct clusters not only on the basis of individual trajectory similarities across time but on the trajectory shape as well. K-Means for longitudinal data using shape-respecting distance has recently been investigated demonstrating higher performance when compared to traditional longitudinal clustering techniques (Genolini C. et al. 2016). Illustrative representation of the longitudinal clustering results will be given as depicted in Figures 14-16.

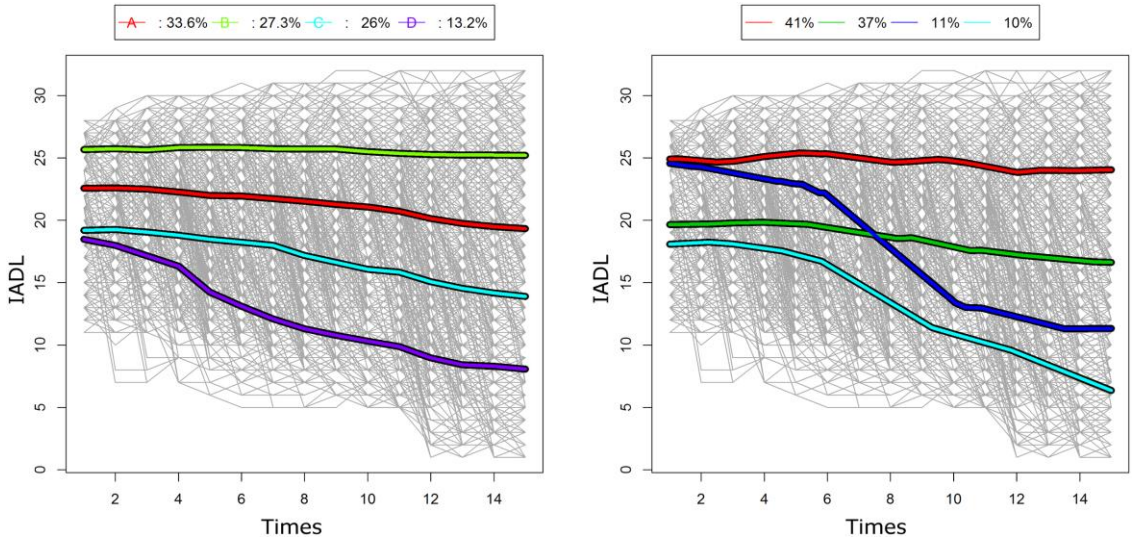

Figure 14. Trajectory clustering for instrumental activities of daily living (IADL) assessment. Left panel: 4 case clusters each displaying distinct trajectory profiles were identified using (conventional) longitudinal clustering techniques. Right panel: kmlShape reveals a rapidly declining cluster (dark blue line) that was neglected using conventional statistical clustering. Image from (Genolini C. et al. 2016).

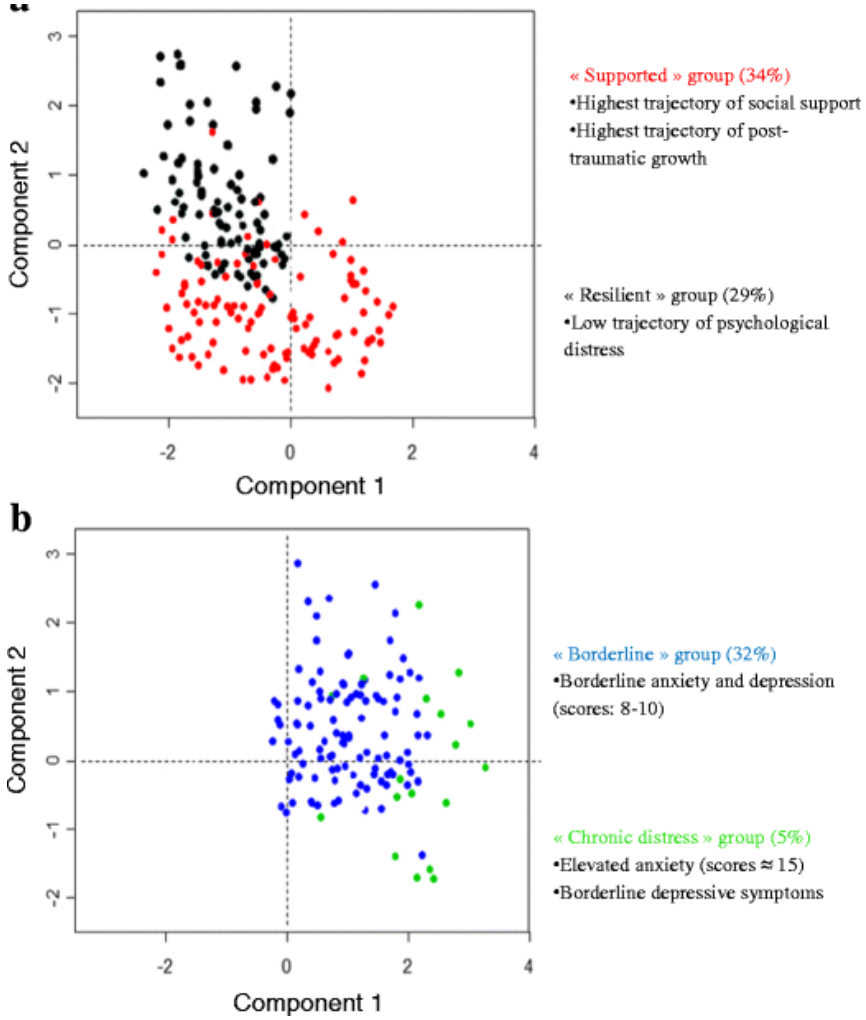

Figure 15. An illustrative representation of trajectory clustering analysis. Four clusters of breast cancer survivors (BCS) were identified on two important resilience dimensions: supportive care needs and psychological distress (Component 1) and degree of social support and posttraumatic growth (Component 2). a) The two clusters

(indicated by black and red dots) of patients displaying varying levels of social support although all patients showed similar (good) levels of illness adaptation. b) Two different clusters (indicated by blue and green dots) of BCS with highest level of needs. Component 1 is positively correlated with trajectories of high needs and high distress (right part of the graph). Component 2 is positively correlated with low social support and posttraumatic trajectories (top of the graph). Image from (A. Brédart et al. 2016).

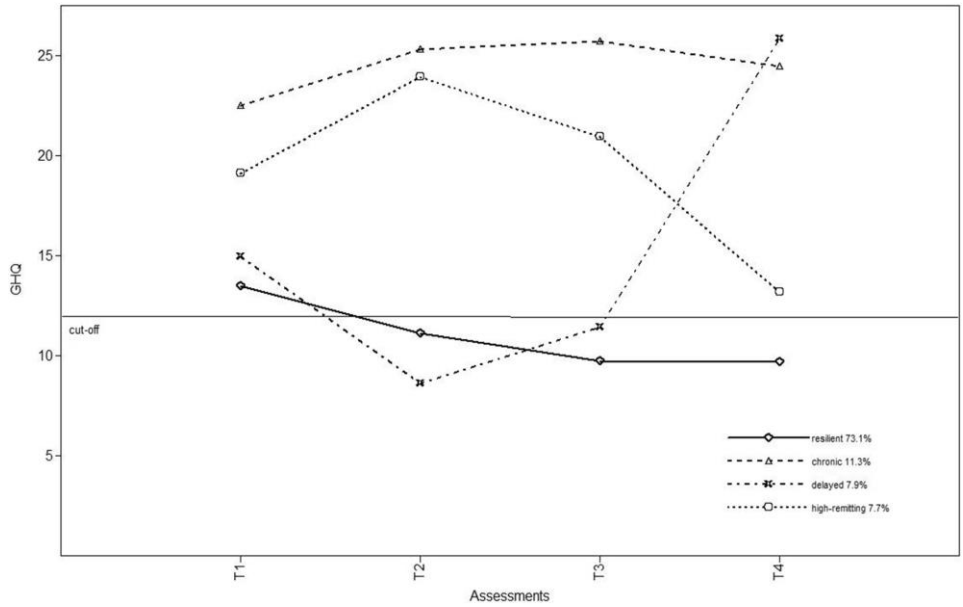

Figure 16. A trajectory based clustering analysis depicting 4 distinct groups using growth mixture modelling. The majority of patients (73.1%) followed a 'resilient' trajectory exhibiting low and gradually decreasing distress level during and after completing cancer treatment. 11.3% of the patients exhibited high distress levels and were assigned to the 'chronic' trajectory. Cluster 'delayed distress' composed of 7.9% of the patients, showed a delayed increase in distress after completion of treatment only, further increasing up to six months. Cluster 'high-remitting' was characterized by high distress levels immediately following diagnosis, further rising during treatment, to resolve only after 6 months following completion. Image from (Kant J. et al. 2016).

4.2.2 Predictive modelling for longitudinal data

Within this analysis, the factors and/or their interactions that can accurately predict final and intermediate outcomes will be identified. The medical and psychological/behavioural factors that will be considered in the longitudinal supervised analysis framework will be assessed at: i) previous time interval, ii) at baseline and previous time interval and iii) across different time intervals within the 18-month follow up period. Towards this direction, the development of the final BOUNCE predictive tool will be achieved by exploiting factors over time. The utilization of longitudinal data in a comprehensive supervised learning scheme will enable the development of a predictive model which will be able to improve its generalization ability in terms of resilience and illness adaptation prediction.

<u>BOUNCE longitudinal supervised learning analysis addressing Clinical scenario IV</u>

Supervised machine learning and conventional statistical methods will be adopted to further exploit and model the longitudinal heterogeneous multiscale data within BOUNCE. This type of analysis will enable the prediction of intermediate and final outcomes related to illness adaptation and resilience. The different patients' profiles in terms of the scores in the medical and psychological/behavioural variables assessed during the follow-up period will be considered for prediction purposes. More specifically, a novel semi-parametric marginal approach (i.e. Boosted Multivariate Trees for Longitudinal Data - boostmtree (A. Pande et al. 2017)) will model all related interactions between BOUNCE medical, psychological, and behavioural factors and

time semi-nonparametrically, and the most important factors and factor-time interactions will be identified using permutation variable importance techniques (Figure 17). Growth-based trajectory modelling will be used to classify patients according to their adaptation/resilience level at final (i.e., at 18 months) and intermediate outcomes (i.e., at 6, 12… months). Several regression models will fit BOUNCE longitudinal data simultaneously and patient-specific probability of group membership will be assigned (Figure 18). Additionally, group-based trajectories will be estimated for each group of patients over time and goodness of fit accuracy will be assessed using C-statistics and Bayesian information criterion (BIC).

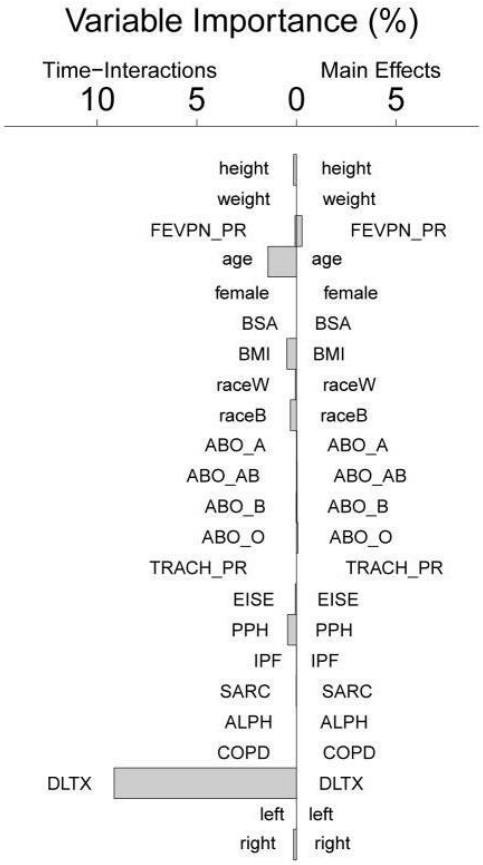

Figure 17. Standardized variable importance for each examined factor using Boosted Multivariate Trees for Longitudinal Data modelling. Top factors are significant factors in terms of affecting the predictive response directly and bottom factors affect the response through time interactions. Image from (A. Pande et al. 2017).

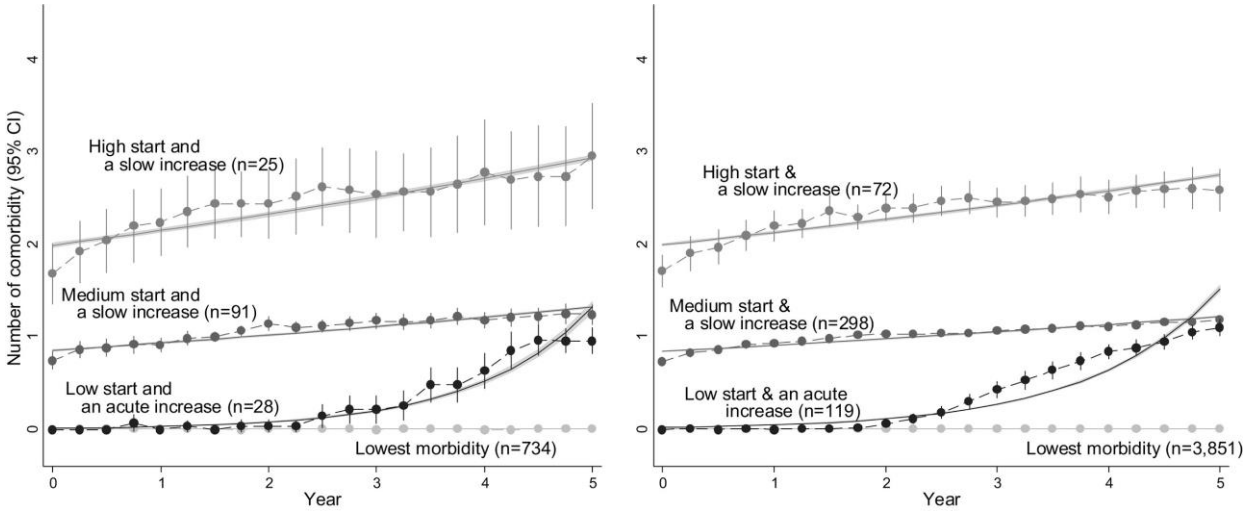

Figure 18. The 4 identified comorbidity trajectories showed similar characteristics (similar observed and predicted values except from the end of follow-up of the 'acute increase' trajectory) with the actual trajectories from cancer survivor and cancer-free subgroups. A constant low trajectory, a low start and an acute increase trajectory, a medium start and a slow increase trajectory, and a high start and a slow increase trajectory were generated. Image from (Hiyoshi A. et al. 2017).

4.3 Theoretical design of the Predictor Model aggregation

Longitudinal predictors of long term outcomes are defined towards the establishment of patient profiles at risk for negative mental/physical health outcomes based on the available information to physicians. Within BOUNCE, the prediction tool includes a limited number of biomedical factors and self-ratings, that will emerge (and be validated) as significant predictors of outcomes in addition to anxiety, depression, and distress which are measured early in the course of the disease. Focusing on end-point outcomes instead of trajectories the predictive outcome will be continuous or categorical. To this end, good outcomes at Tn regardless of prior status imply indirectly high resilience, whereas poor outcomes imply low resilience as has been defined in BOUNCE.

Concerning the cross-sectional analyses within WP4 and the theoretical predictor model aggregation, different population groups at single time points are compared. Using cross-sectional data different types of predictors are developed from a single time point, or combined sets of predictors are designed from multiple time points. Towards this direction traditional machine learning techniques are applied to predict a specific clinical outcome (mental health, QoL, etc.). The main scope of the current analysis is the development of a decision level fusion model from all clinical predictive outcomes (probabilistic soft outcomes) to investigate whether the ensemble of the decisions further improves prediction of resilience at a specific time point. The classifiers that are developed are coupled with variable selection techniques in order to extract the most informative features for each data view in terms of models performance and evaluation (Figure 19). Subsequently, fusion takes place at the decision level in order to achieve better generalization performance in comparison to single machine learning algorithms.

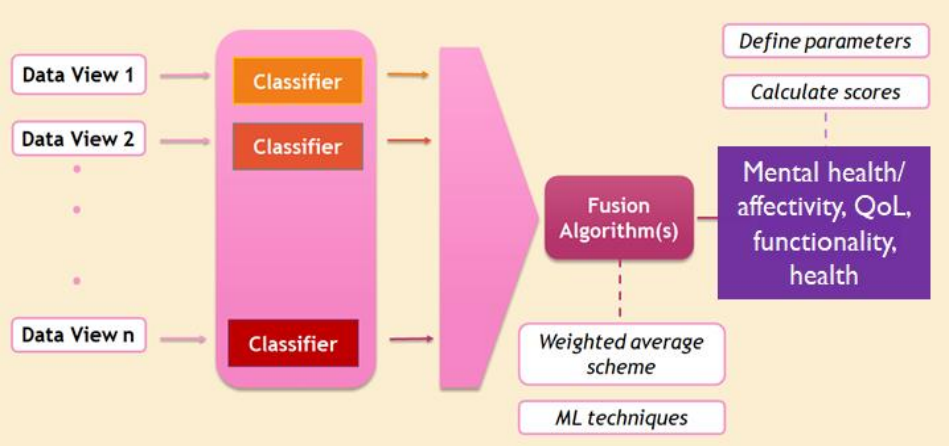

Figure 19. The models' fusion pipeline that will be followed within BOUNCE for aggregating the different decisions made by individual classifiers.

The fusion model within BOUNCE is implemented by utilizing ensemble methods which combine the predictions of several base estimators. The base estimators are built with given learning algorithms, such as generalized linear models, random forests, extreme gradient boosting, support vector machines-SVM, etc., in order to improve the performance compared to a single estimator. Voting classifier (Ruta, D et al. 2005, Kuncheva, L. I. et al 2003) is applied for combining conceptually different machine learning classifiers and use a majority vote ("hard" vote) or the average predicted probabilities ("soft" vote) to predict the class labels. Such a classifier can be useful for a set of equally well performing supervised or unsupervised models in order to balance out their individual weaknesses. With the ensemble vote classifier different training sets are considered for building the predictive models (Figure 20). As mentioned above, different classification algorithms are adopted for predicting the class label of new samples. Voting classifier will be applied for making the final and more robust prediction of the end-point outcomes.

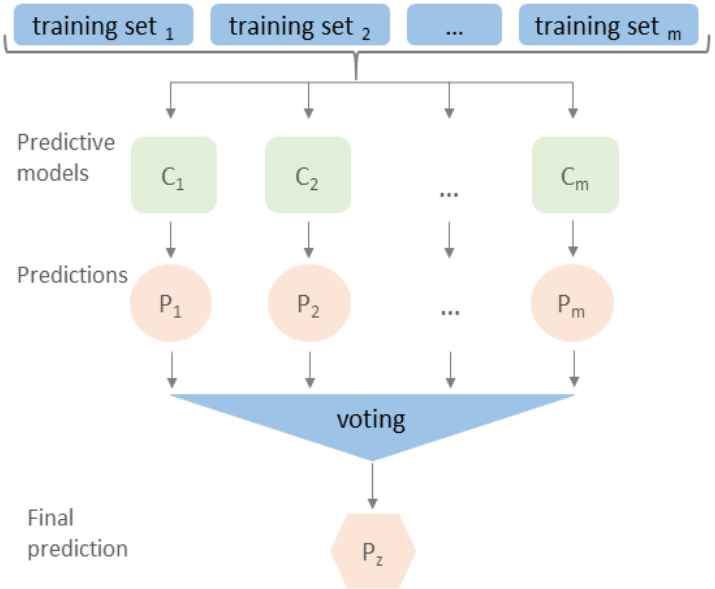

Figure 20. The process followed by an ensemble voting classifier for combining the different predictions and make the final prediction in terms of voting. Different training sets are considered for each classifier in order to build the predictive models before their fusion.

Implementation of the majority voting EnsembleVoteClassifier for prediction purposes within BOUNCE is done in Python 3.6 by utilizing the EnsembleVoteClassifier in the mlxtend python library (Raschka, S. 2018.). We implement the EnsembleVoteClassifier in terms of "hard" and "soft" voting. In hard voting, the final class label is predicted as the class label that has been predicted most frequently by the prediction models. In soft voting, we predict the class labels by averaging the class-probabilities.

5. Integration methodology of the in-silico trajectory

This section gives an overview of the technological integration of the prediction models in BOUNCE platform. More specifically, all models that will be developed in the context of the BOUNCE project will be hosted in the BOUNCE Model Repository. The BOUNCE In Silico Prediction Repository will be capable of persistently storing the predictions of the models developed within the BOUNCE project. Finally, security aspects are discussed. More details can be found in deliverables D5.1 BOUNCE Conceptual & Reference Architecture and D5.2 Platform Design.

5.1 Model Repository

Model Repository (MR) is a web application that will store the in-silico resilience trajectory predictor and any other prediction model developed within BOUNCE lifetime. The key entities of the MR are the model, the parameters, the properties, the property values, the files, and the references. The model entity includes all the descriptive information of a model. The parameters entity contains all the information regarding the input parameters needed for the execution of the model (data type, units, description etc.) as well as the output data of a model (description, type etc.). The property entity contains the properties that could characterize a model (e.g. based on the statistical and machine learning techniques that were used, the stochastic or deterministic nature of the model) and the file entity contains the files linked to the model (e.g. executable, documentation etc.). Finally, the reference entity contains any references associated with the model.

Following the development of a model, the modeller is requested to upload it on the BOUNCE platform by distinctly storing each and every one of the aforementioned entities of a model in the MR. Persistent storage is thus provided and the model is enabled to participate in the process of producing predictions according to the workflows described in D5.1 BOUNCE Conceptual & Reference Architecture.

Specifically,

- The Decision Support System (DSS) requests and retrieves model information and model parameters specifications from MR.

- Execution Engine (EE) requests and retrieves the model (executable) from MR in order to run the requested analysis.

Both EE and DSS are presented in detail in D5.1 BOUNCE Conceptual & Reference Architecture.

MR is also integrated with the Access Controller (AC), a component providing access to the repository and subsequently to the models only to authenticated users of the platform having specific roles (see subsection 5.3).

5.2 In Silico Prediction Repository

The BOUNCE In Silico Prediction Repository is a web-based application, capable of persistently storing the predictions of the models developed within the BOUNCE project. The input and output data of each simulation will be persistently stored after the completion of the simulation scenario. Information related to the input (disease characteristics, sociodemographic variables, and emotional status self-ratings, etc.) and output (mental health, quality of life, level of resilience of women with breast cancer etc.) of all the simulations conducted using the models developed in the context of BOUNCE will be readily available through the ISPR for evaluation, comparison and validation. Simulation results that are produced by EE are stored in ISPR via the provided API. ISPR provides the stored results to DSS so that the clinician is enabled to view the prediction outcome, identify patients at risk for poor psychosocial and functional outcomes at any point during the course of diagnosis and treatment for breast cancer and take corrective actions, if need be.

ISPR interacts with EE and DSS in the following ways:

- EE stores the model input and output to ISPR.

- DSS retrieves the model execution results.

Both EE and DSS are presented in detail in D5.1 BOUNCE Conceptual & Reference Architecture.

ISPR is also integrated with AC i.e. the component providing access to the repository and subsequently to the predictions of the models only to authenticating users of the platform having specific roles (see subsection 5.3).

5.3 Security integration

The BOUNCE framework, as described also in deliverable D5.1 (‘BOUNCE Conceptual and Reference Architecture’), adopts the principle of security by design towards the aim of safeguarding the personal and sensitive information that is incorporated within the framework. Hence, this principle is adopted by all implemented software modules within the BOUNCE framework, including both the model repository that will contain and store the developed models, as well as the developed models themselves.

With regards to the model repository, a comprehensive description of the security aspects has been documented within the context of deliverable D5.2 (‘Platform Design’) of WP5. In a nutshell, the realisation of the security by design is based on two basic pillars: a) the data access control and b) the security of data in storage, the security of data in transit and the security of the technical interfaces. The access control is realised with the help of the Access Controller component that is controlling the access to the repository, as well as to the models that are stored in the repository with the suitable authentication and authorisation mechanism. This mechanism is based on the Role Based Access Control paradigm and implements a token based authentication approach based on JSON Web Token (JWT) in order to formulate an access control decision. For the security of data in storage a two-fold approach is followed: a) the utilisation of checksum that is safeguarding the integrity and security of the stored data and b) the security mechanisms of the underlying storage solution. The security of data in transit is ensured with the use of the Secure Socket Layer (SSL) and Transport Layer Security (TLS) that is enabling the secure communication between the interacting components. Finally, the security of the technical interfaces is enabled through the utilisation of the JWT with the support of the

Access Controller towards the effective authorisation, authentication, and access control enforcement.

While the described mechanisms are safeguarding the security aspects of the model repository, it is crucial that the security aspects of the developed models stored in the repositories are covered also. Furthermore, the nature of this specific software module requires a different approach in order to adopt the security by design principle of the BOUNCE framework.

As described in the previous sections, the implementation of any computational model requires access to a variety of data and the implementation of various functions or algorithms. For this reason, in order to ensure the security aspects of the BOUNCE framework an additional process will be adopted. More specifically, each model is designed and implemented by adopting the following guidelines and principles:

- Access to the various data that are utilised during any execution phase of the model must be performed via the respective API that is provided by the BOUNCE platform for accessing the underlying data lake. The respective API is safeguarded with the help of the Access Controller component ensuring legitimate access on the underlying data resources stored in the data lake.
- Deletion operations on any data resource is not permitted.
- Connections, both incoming or outgoing, to any external server or service outside of the BOUNCE framework and data transfer is not permitted.
- Data downloading in the local environment during the model execution is not permitted.
- The execution of any command that requires privileges escalation in the system (i.e. sudo commands) is not permitted.

The described guidelines and principles ensure that the security by design principle of the BOUNCE framework is properly adopted and all the security requirements of the BOUNCE framework are met.

6. Trajectory analysis (Longitudinal Clustering): Application of advanced statistical methods to the BOUNCE data

In paragraph 4.2.1 a methodological framework is being described for the identification of clusters of individuals that follow similar developmental trajectories, i.e. similar patterns of change in psychological or behavioral outcomes across multiple (i.e., at least three) time points. Within this framework the aim is threefold: a) modelling of the mean growth curves of the generated distinct subpopulations, b) identification of psychosocial and behavioural variables that contribute to the prediction of the generated trajectory groups and c) building of predictive models of long term development of resilience. In the following sections, an overview of the main statistical approaches for the clustering of trajectories are presented and practical issues related to their application are discussed. Furthermore, this framework is currently being applied to the retrospective data from the BOUNCE clinical partners to identify systematic sources of individual differences of patient resilience progress over time. Indicative results are presented here.

6.1 Challenges in the analysis of longitudinal data

For two time points, a simple change score can be computed and the data can be analysed using methods for cross-sectional data, such as ANCOVA (Hedeker & Gibbons, 2006). For balanced designs, i.e. when the number of time points n is the same for all subjects, traditional ANOVA or MANOVA models for repeated measurements (i. e., traditional mixed-effects models or

multivariate growth curve models) can be used to analyse change over time of a longitudinal Gaussian outcome and assess the effect of covariates on it. However, longitudinal data collected in cohort studies, such as the one of BOUNCE, may be too complex to enter the framework of conventional methods [Gibbons et. al., 2010; Proust-Lima et al. 2017] for the following reasons:

- Difficult Distributions: The longitudinal outcomes are not necessarily Gaussian but possibly binary (e.g., classifications of whether or not an individual has met diagnostic criteria for a given disorder or dichotomous data), ordinal (e.g. psychological scale), zero inflated Poisson (e.g., where a large number of individuals have no symptoms and the remaining individuals experience one or more symptoms), or continuous but asymmetric.
- Missing Data: may be due to attrition, (i.e. subjects dropping out of the study and not returning), or may be sporadic or intermittent (i.e., subjects with missing data between observed time points).
- Not only one but several longitudinal outcomes may be collected, especially when the interest is in a psychological process that cannot be measured directly (e.g., quality of life, resilience).
- The longitudinal process may be altered by the occurrence of one or multiple times-to event (e.g. disease progression).
- Irregularly Spaced Measurement Occasions: It is common in real longitudinal studies for individuals to vary in the number of repeated measurements they contribute and even in the time at which the measurements are obtained. This may be due to dropout or simply due to different subjects having different schedules of availability.
- Subjects Clustered in Centers: The clustering of individuals within ecological units (e.g. clinics, hospitals, countries, etc.) produces an additional source of correlation that violates the independence assumption of traditional fixed-effects models.
- Non-observed heterogeneity may exist in the population.

A review of the current literature reveals that in psychology and medicine, including breast cancer research (Table I), two statistical approaches have been widely utilized for identifying meaningful groups or classes of individuals within a larger heterogeneous population: the growth mixture modelling (GMM) and the latent class growth analysis (LCGA). Both approaches share the common goal of modelling individual-level heterogeneity in time series data.

Table I Overview of the reviewed literature categorized by trajectory analysis method as well as by the fit criteria used in each study.

Paper	**Method**		**Information Criteria**			**Entropy**	**LRT**	
	LCGA	GMM	BIC	ABIC	AIC		VLMR	BRT
Bidstrup et al. 2015	+	-	+	-	+	-	-	-
Danhauer et al. 2015	+	-	+	+	-	-	-	-
Brunet et al. 2014	-	+	+	-	+		+	-

Donovan et al. 2014	-	+	+	-	-	-	+	+
Dunn et al. 2011	-	+	+	-	-	-	-	-
Helgeson et al. 2004	+	-	+	-	+	-	-	-
Henselmans et al. 2010	-	+	+	+	+	+	+	+
Lam et al. 2010	-	+	+	+	+	+	+	+
Lam et al. 2013	+	-	+	-	+	-	-	-
Rottmann et al. 2016	+	-	+	-	-	-	-	-
Wang et al. 2014	+	-	+	-	-	-	-	-

ABBREVIATIONS: LCGA: Latent Class Growth Analysis, GMM: Growth Mixture Modeling, BIC: Bayesian Information Criterion, ABIC: Adjusted Bayesian Information Criterion, AIC: Akaike Information Criterion, VLMR-LRT: Vuong-Lo-Mendell-Rubin Likelihood Ratio Test, B(L)RT: Bootstrap (Likelihood) Ratio Test

Conventional growth curve modelling (GCM) techniques (e.g. hierarchical modeling (Bryk & Raudenbush 1987, Goldstein 1995) and latent curve analysis (McArdle & Epstein 1987, Meredith & Tisak 1990, Muthén 1989,Willett &Sayer 1994)) estimate a single trajectory that averages the individual trajectories of all participants in a given sample [Andruff et al 2009, Nagin 2010]. More practically speaking, GCM approaches assume that individuals are drawn from the same population and that development over time can be mapped using one set of parameters. Time or age is used as an independent variable. The trajectory is modelled assuming a polynomial function (i.e., linear, quadratic, or cubic) of time or age. This average trajectory contains an averaged intercept (i.e., the expected value of the dependent variable when the value of the independent variable(s) is/are equal to zero) and an averaged slope (i.e., a line representing the predicted strength and direction of the growth trend) for the entire sample. This approach captures individual differences by estimating a random coefficient that represents the variability surrounding this intercept and slope. Subsequently, categorical or continuous, time varying or invariant covariates, representing potential risk or protective factors, can be incorporated into the model (conditional modelling) to examine whether individual differences in the intercept and/or slope values can be predicted. Furthermore, by centering the age or time variable, a researcher may set the intercept to any predetermined value of interest.

GMM was proposed by Muthén and Shedden in 1999. GMM is an elaboration of GCM based on finite mixture models, so that two or more growth curve models are used to model population variability in developmental trajectories. It is a method for identifying multiple unobserved sub-

populations, describing longitudinal change within each unobserved sub-population, and examining differences in change among them. More specifically, the parameters of the model provide information about the mean change, extent of interindividual differences in change, and pattern of change for the unobserved groups believed to compose in the data, and, for each individual, the probability that he or she belongs to each of those groups. Its defining feature is the allowance of random effects within classes, that is, within-class heterogeneity in patterns of change (Ram & Grimm, 2009; Hipp & Bauer, 2006). The framework of growth modeling GMM is embodied in the MPlus software (Muthén and Muthén, 2001).

LCGA (or group-based trajectory modelling (GBTM)) is a special type of GMM, whereby the variance and covariance estimates for the growth factors within each class are assumed to be fixed to zero. By this assumption, all individual growth trajectories within a class are homogeneous; i.e. individuals within a class are assumed to follow precisely the same trajectory (apart from random errors). One advantage of this more restricted specification is that it is simpler to allow for response scales other than the continuous normal (e.g., binary outcomes with a logit or probit link) (Hipp & Bauer, 2006); on the other hand, a disadvantage is that fitting an overly restrictive model can lead to the estimation of spurious classes (Hipp & Bauer, 2006; Bauer & Curran, 2004). This framework of growth modelling has been developed by Nagin and colleagues (Nagin & Land, 1993,; Nagin, 1999). The zero constraints on the variance estimates in LCGA approach allow for faster model convergence (Kreuter & Muthén, 2007; Jung & Wickrama, 2008). Furthermore LCGA can serve as a starting point for conducting GMM (Jung & Wickrama, 2008). LCGA is embodied in the SAS procedure Proc Traj (Jones, Nagin, & Roeder, 2001). LCGA models can also be easily implemented in Mplus.

An alternative GMM approach has been developed by the R community (Proust-Lima et al. 2017). The R package lcmm (full title: Extended Mixed Models Using Latent Classes and Latent Processes) provides a series of functions that extend the linear mixed model to various settings including specific types of nonlinear mixed models and multivariate mixed models, but also latent class mixed models and joint models. The latent process mixed model is designed for the longitudinal analysis of scales that usually have asymmetric distributions with possibly a ceiling effect, floor effect and unequal interval scaling. In particular, lcmm package includes the estimation of mixed models and latent class mixed models for Gaussian longitudinal outcomes, curvilinear and ordinal univariate longitudinal outcomes and curvilinear multivariate outcomes, as well as joint latent class mixed models for a (Gaussian or curvilinear) longitudinal outcome and a time-to-event outcome that can be possibly left-truncated right-censored and defined in a competing setting. Maximum likelihood estimators are obtained using a modified Marquardt algorithm with strict convergence criteria based on the parameters and likelihood stability, and on the negativity of the second derivatives. The package also provides various post-fit functions including goodness-of-fit analyses, classification, plots, predicted trajectories, individual dynamic prediction of the event and predictive accuracy assessment.

Approaches based on mixed regression modelling pose no restrictions on the number of observations per individual. The missing data are not imputed; rather the model parameters are estimated using all available data (Hedeker & Gibbons, 2006). Furthermore, MRMs allow for the presence of time varying and invariant covariates. It should be noted that the more advanced models (e.g., generalized mixed-effects regression models) that are appropriate for analysis of unbalanced longitudinal data are based on large sample theory and may be inappropriate for analysis of small N studies (e.g., N < 50) (Hedeker & Gibbons, 2006).

To summarize, if it is assumed that all individuals in the population follow a similar functional form of development, then GCMs may be sufficient to capture interindividual variability in change across time. However, if one trajectory shape is not assumed to "fit all," then the LCGA and GMM approaches described above will likely provide a better fit to the research question and have the secondary benefit of better fitting the data (Nagin & Odgers, 2010). The following types of trajectories analysis can be identified (Proust-Lima et al., 2017; Nagin & Odgers, 2010; Proust-Lima et al., 2014):

- *Exploration of unconditioned and unadjusted trajectories*: no covariates in the mixture model & the class-membership model are considered (raw heterogeneity).
- *Exploration of unconditioned adjusted trajectories*: covariates are considered only in the mixture model. In this case residual heterogeneity after adjustment for known factors of change over time is investigated.
- *Exploration of conditioned unadjusted trajectories*: covariates are incorporated in the class-membership model. In this case heterogeneity is explained by 'targeted' factors.
- *Exploration of conditioned and adjusted trajectories*: covariates are incorporated in both the class-membership model & the mixed model. In this case residual heterogeneity is explained by 'targeted' factors.
- *Multitrajectory Modeling:* to model the developmental course of two distinct but related outcomes.
- *Joint modelling* approach consists in defining: (1) a model for the time-to-event, usually hazard model, (2) a model for the marker trajectory, usually a mixed model, and (3) linking both models using a shared latent structure.

6.2 Model selection

Model selection refers to the identification of the most suitable GMM or LCGA model that provides the most reasonable representation of the data in terms of the optimal number of latent classes and the type and extent of differences between and within these classes (Ram and Grimm, 2009). The most commonly used fit indices are presented below.

Models can be compared using relative fit information criteria such as the Bayesian Information Criterion (BIC), the Akaike Information Criterion (AIC) and the Adjusted Bayesian Information Criterion (ABIC). Lower values on these information criteria indicate better-fitting models. Furthermore, models can be evaluated with respect to the accuracy or, more aptly, confidence with which individuals have been classified as belonging to one group or another. Entropy is an increasingly used summary indicator, which averages the posterior probabilities of individuals' group membership. Values closer to 1 indicate greater precision (range 0 to 1). Comparisons can also be made on an array of likelihood ratio tests that quantify specific comparisons between the models of interest and a model with one fewer class. These tests include the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR-LRT), the adjusted Lo-Mendell-Rubin likelihood ratio test, as well as the bootstrap likelihood ratio test (BLRT) (Nagin & Odgers 2010; Ram and Grimm, 2009). For example, significant p-values of VLMR-LRT test suggest that the estimated model fits the data better than a model with one fewer groups.

In terms of model adequacy, Nagin (2005) lays out the following criteria: (a) obtaining for each trajectory group a close correspondence between the estimated probability of group

membership and the proportion assigned to that group based on the posterior probability of group membership, (b) ensuring that the average of the posterior probabilities of group membership for individuals assigned to each group exceeds a minimum threshold of 0.7, (c) establishing that the odds of correct classification based on the posterior probabilities of group membership exceed a minimum threshold of 5, and (d) observing reasonably tight confidence intervals around estimated group membership probabilities.

However, model selection should not be based solely on formal statistical criteria (Nagin & Odgers 2010). The goal is to end up in trajectory groups distinguishable in terms of pre-existing characteristics, subsequent outcomes, their response to treatment, or their relationship to trajectories for other outcomes, whatever methodology one may choose (Nagin & Odgers 2010).

In mixture modelling, initial values are crucial for the correct convergence of the program. In this type of modelling, parameters are estimated by the method of maximum likelihood and are iterative in nature (e.g., EM algorithm) (Jung & Wickrama, 2008). Ideally, the iteration will result in successful convergence on the global maximum solution, that is, the parameter estimates associated with the largest log likelihood. However, the log-likelihood may have multiple maxima, and algorithms based on maximization of the likelihood might converge to local maxima (Redner and Walker 1984). This means that convergence towards the global maximum of the log-likelihood is not ensured when running the algorithm once. To ensure the convergence to the global maximum, the model should run several times from different sets of initial values (typically from a grid of initial values) (Proust-Lima et al. 2017).

6.3 Trajectory Analysis of the two available retrospective datasets

6.3.1 Overview of the HUJI dataset

A detailed description of the dataset can be found in D4.1. The dataset originates from a study conducted by the Hebrew University of Jerusalem designed to evaluate the long-term effect of group intervention in female patients with early-stage breast cancer (Hamama-Raz et al. 2012, 2016, Pat-Horenczyk et al 2015, 2016). Participants were patients 25–75 years of age who had completed adjuvant therapy (chemotherapy, radiotherapy) at least three months prior to study participation.

The current longitudinal analyses involve the following psychological data collected at eight time points, i.e. baseline, month 3, month 6, month 12 and month 24:

- **Posttraumatic stress symptoms:** The Posttraumatic Stress Diagnostic Scale (PDS; Foa, Cashman, Jaycox, & Perry, 1997)
- **Functional impairment**: The items were derived from the Diagnostic Interview Schedule for Children (Lucas et al. 2001), according to Criterion F of the DSM – IV – TR – designed for the specific clinical study.
- **Depressive symptoms:** The Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977).
- **Cognitive and emotion regulation:** The Cognitive Emotion Regulation Questionnaire (CERQ) (Garnefski & Kraaij, 2006).
- **Coping flexibility:** The Perceived Ability to Cope with Trauma (PACT) scale (Bonanno, Pat-Horenczyk, & Noll, 2011).
- **Posttraumatic growth:** The Posttraumatic Growth Inventory (PTGI; Tedeschi & Calhoun, 1996).
- **Ego Resilience** (Block & Kremen, 1996).

- **Feeling Today**: Three overall assessments of distress level, level of perceived resilience, and amount of hope for the future – designed for the specific clinical study.

The analyses refer to a subgroup of 129 patients with psychological measures on at, at least, two time points, over the 2-year period. The total scores were considered (mean values). Furthermore, subscale scores were calculated at baseline, whenever applicable. The analyses also consider the following background data at baseline:

- Demographics: age, country of birth, marital status, number of children, work status, source of income, place of residence, workshop participation, Israeli born
- Medical parameters: stage, treatment type (chemo or/and radio), hormonal therapy, Herceptin, treatment protocol, genetic test, family history
- Symptoms: heat waves, mood swings, sleep problems, obesity, discomfort with their body, disruption in sexuality, interference with a sense of femininity.

Table II

Instrument		No Items	Scale	Total score	Subscales	Cut offs	References
CES-D	Depressive symptoms	20	0-3	0-60	I - Depressed affect:3,6,14,17,18,9,10 II – Positive affect : 4,8,12,16 III – Somatic symptoms: 1,2,7,11,20,5,13 IV – Interpersonal: 15,19	<16 Not depressed >=16 Depressed	Radloff 1977
PTGI	Post traumatic growth	21	0-5	0-105	I - Relating to Others: 6, 8, 9, 15 16, 20, 21 II - New Possibilities:3, 7, 11, 14, 17 III - Personal Strength: 4,10,12,19 IV - Spiritual Change: 5,18 V - Appreciation of Life: 1,2,13	No cutoffs	Tedeschi and Calhoun 1996
PTGI-SF	Post traumatic growth - Short Form	10 (8,20,7,11,10,19,5,18,1,2 of PTG)	0-5	0-50	In respect to PTG: I - Relating to Others: 8, 20 II - New Possibilities: 7, 11 III - Personal Strength: 10, 19 IV - Spiritual Change: 5,18 V - Appreciation of Life: 1,2	No cutoffs	
EGO	Resilience	14	1-4	14-56	-	0-10 Very low 11-22: Low Resilience Trait 23-34: Undetermined 35-46: High 47-56: Very high	Block & Kremen, 1996
CERQ	Cognitive Emotion Regulation	18	1-5	-	Positive regulation: 1+3+5+7+8+11+12+13+15+16 (acceptance, positive refocusing, refocus on planning, positive reappraisal, and putting into perspective) Negative regulation: 2+4+6+9+10+14+17+18 (self-blame, rumination, catastrophizing, and other blame)	No cut offs	Garnefski & Kraaij, 2006

PACT	Coping Flexibility	20	1-7	-	A - Forward Focus: 1 + 2 + 3 + 4 + 5 + 8 + 9 + 13 + 15 + 16 + 17 +18 B - Trauma Focus: 6 + 7 + 10 + 11 + 12 + 14 + 19 + 20 Total coping: (Average of Factor A + average of Factor B) Polarity: (abs|Average of Factor A - average of Factor B|) Discrepancy: (Average of Factor A - average of Factor B) Flexibility: total coping – polarity	No cut offs	Bonnano et al. 2011
PDS	Post traumatic stress symptoms	17	0-3	0-51	Re-experiencing: 1 + 2 + 3 + 4 + 5 (Items 22-26) Avoidance: 6 + 7 + 8 + 9 + 10 + 11 + 12 (Items 27-33) Arousal: 13 + 14 + 15 + 16 + 17 (Items 34-38)	0: no rating 1–10: mild 11–20: moderate 21–35: moderate to severe >36: severe	Foa 1977

6.3.2 Overview of the HUS dataset

A detailed description of the dataset can be found in D4.1. The dataset originates from a study conducted by Helsinki University Hospital Comprehensive Cancer Center, Finland designed to evaluate whether physical exercise training improves the quality of life (QoL) and physical fitness of breast cancer survivors. (Saarto et al. 2012). Participants were patients 35–68 years of age who on average last chemotherapy cycle and radiotherapy session took place approximately 11.6 and 4 weeks (mean values) prior study participation. The current longitudinal analyses involve the following psychological data collected at eight time points, i.e. baseline, month 3, month 6, month 12, month 18, month 24, month 30 and month 36:

- **EORTC QLQ- C30:** It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
- **EORTC QLQ- BR23**: It comprises body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss.
- **WHQ** women's health questionnaire.
- **FACIT-F** - Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire.
- **BDI** - Beck Depression Inventory short form: Finnish modified version of Beck's 13-item depression scale (**R-BDI**).

The analyses refer to a subgroup of 516 patients that have psychological measures at, at least, two time points, over the 3-year period. The subscale scores were considered. The analyses also consider the following background data at **baseline**:

- **Clinical data:** age, WHO class, menstruation after chemotherapy, menopausal status, menopause age, BMI, weight, height, bone mineral density, total kolesterol levels, Blood Glucose, Blood Pressure, pulse, any other disease also psychiatric, basic health status, disability status, physical pain

- **Breast and treatment data:** tumour size, pT, pN, histological type, metastatic lymph modes, receptor status (estrogen, progesterone), Her2 expression, type of breast surgery, type of axillary operation, type of treatment (herceptin, chemotherapy, radiotherapy, endocrine treatment)
- **SocioDemographics:** years of education, marital status, number of children, employment status, reason for not working
- **History and Life Style:** competing athlete, smoking, frequency and amount of alcohol consumption, reduced fat in the diet, increased vegetables, increased the amount of exercise etc.

Physical performance and activity: mean figure 8 running, mean 2-km walking test, leisure time physical activity, self-reported physical activity, MET (metabolic equivalent)

6.4 Mixed-effects linear regression analysis: Covariate effect on average trajectory

6.4.1 HUJI dataset

Analysis plan

A mixed-effects linear regression analysis was performed in order to analyze the change over time of the psychological outcomes CERQ, PACT, PTGI, EGO, CES-D, PDS, functional impairment and the levels of distress, hope and resilience over the 2-year observation period. Subsequently, the effect of sociodemographic, medical variables and self-reported symptoms at baseline on the average trajectory of the previously mentioned psychological measures was assessed. The analysis was performed using lcmm package of R.

Results

Rate of change (slope) is statistically different from zero for stress today, posttraumatic stress symptoms, posttraumatic growth, EGO resilience, depression and negative cognitive-emotion regulation (Table III). Stress, stress symptoms, depression and negative cognitive-emotion regulation are improving across time, whereas posttraumatic growth and resilience are increasing. However, the slope is small in all cases and the average change over the two year period ranges approximately between 5-25%. The spaghetti plots and the regression lines that approximates the average trajectory for indicative psychological outcomes are depicted in Figure 21, Figure 22.

Table III Results of the mixed-effects linear regression model for each psychological outcome with only time as a regressor. Time is treated using incremental values from 0 to 4. The estimated regression coefficient of the slope and the p-value of the Wald test are reported. Color density is proportional to significant levels 0.001, 0.01 and 0.05.

	Intercept	Slope: linear term	Slope: quadratic term	Wald test for slope: p-value
Stress today	2.588	-0.323	0.037	0.0068
Resilience today	5.561	0.147	-0.026	0.4467
Hope today	6.024	-0.059	0.005	0.5211
PACT Average coping flexibility	5.294	-0.027	0.006	0.9280
PTGI Posttraumatic growth	3.259	0.143	-0.027	0.0048
EGO Resilience	3.029	0.011	0.006	0.0024
PDS Posttraumatic stress symptoms	0.832	-0.049	0.005	0.0350
Functional impairment	1.055	-0.014	-0.009	0.1404
CES-D Depression	0.720	-0.042	0.005	0.0919
CERQ Positive cognitive emotion regulation	3.349	0.056	-0.007	0.3675
CERQ Negative cognitive emotion regulation	2.276	-0.084	0.011	0.0438
PACT Forward focus	5.404	-0.059	0.013	0.7534
PACT Trauma Focus	5.132	0.011	-0.001	0.9632
PACT Total flexibility	9.722	0.044	-0.001	0.7863

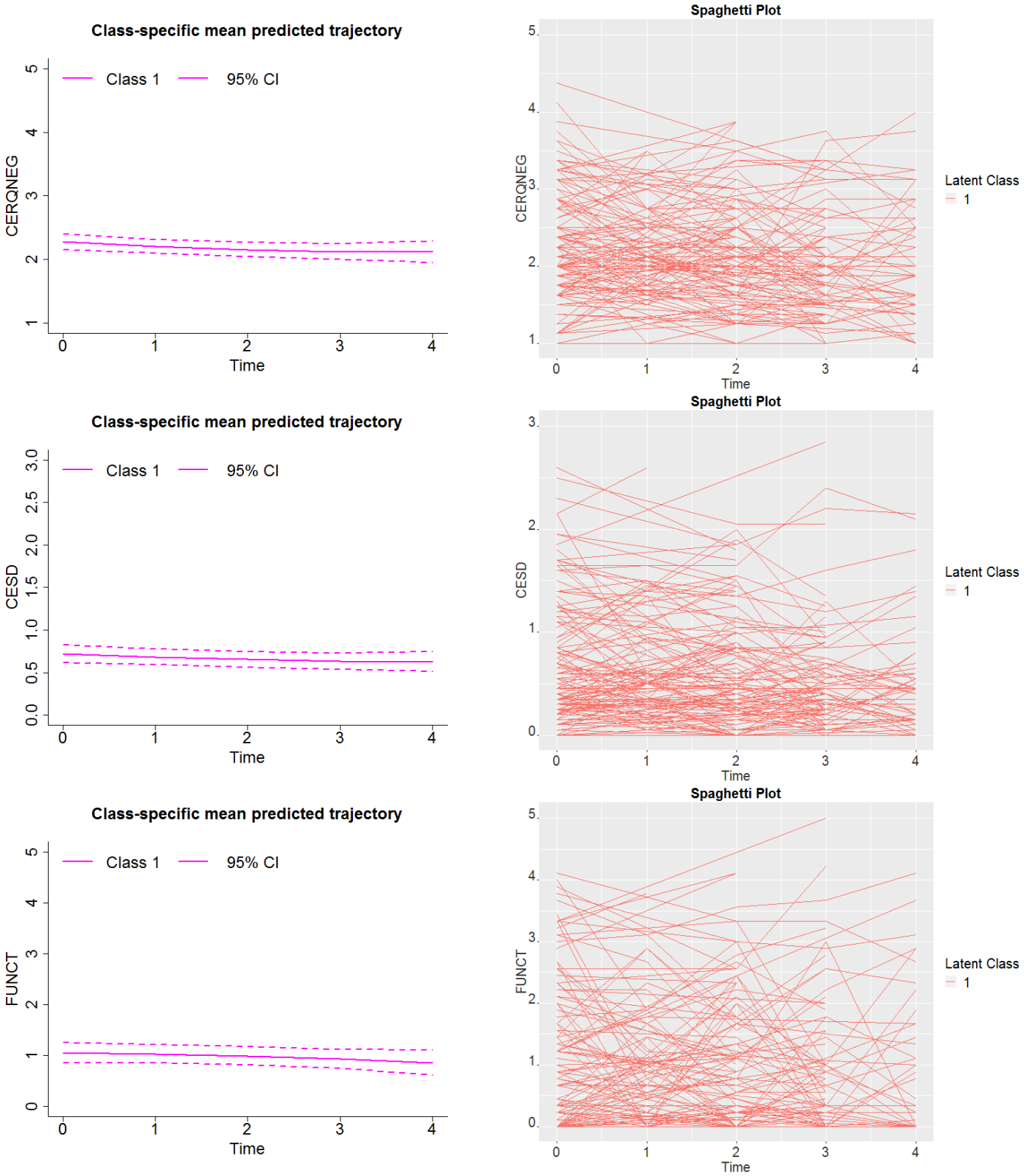

Figure 21 Mean predicted trajectories and spaghetti plots (each thin line connects the responses for the same patient over time) for indicative psychological outcomes. Coding: Time 0:baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 24 months.

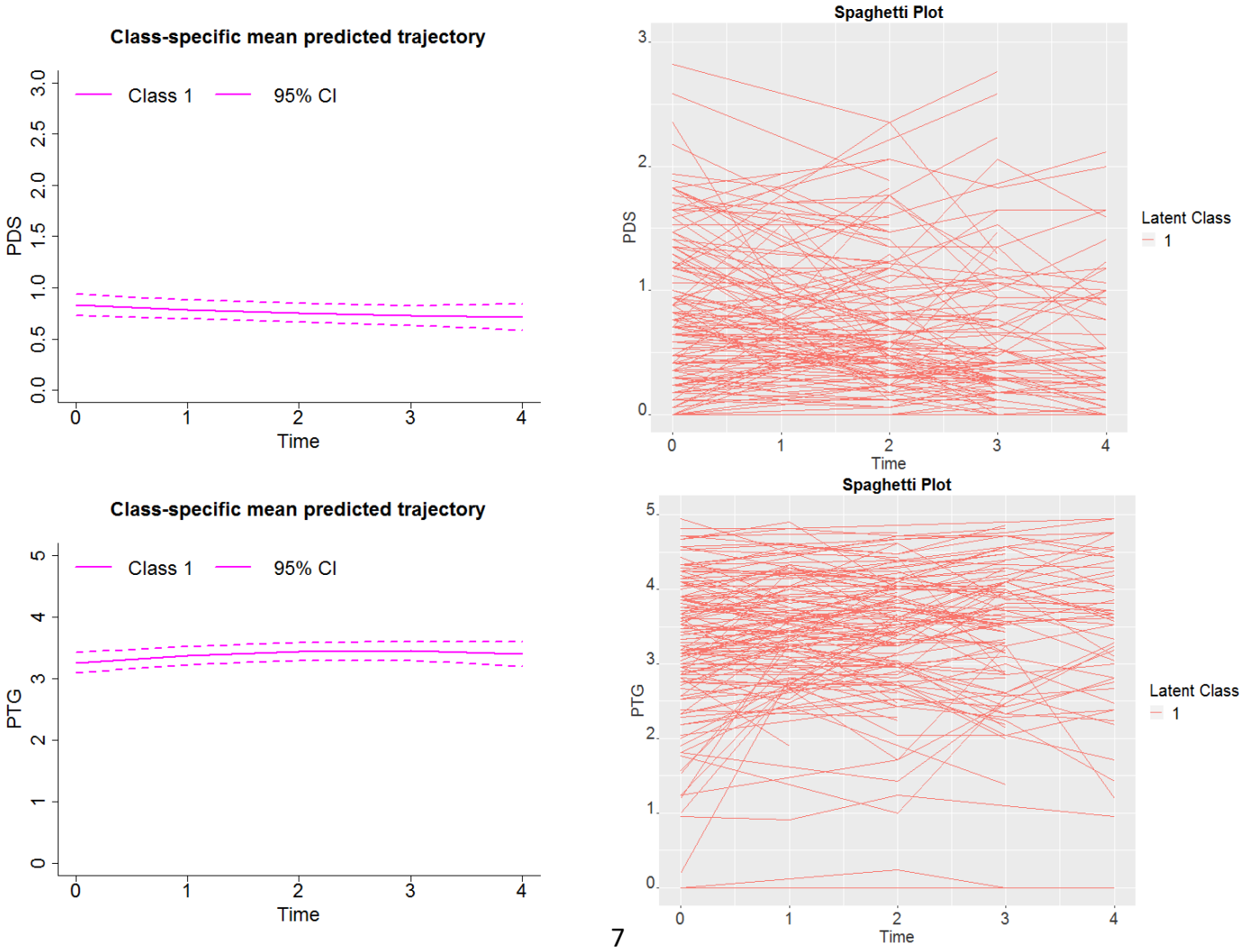

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Figure 22. Mean predicted trajectories and spaghetti plots (each thin line connects the responses for the same patient over time) for indicative psychological outcomes. Coding: Time 0: baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 24 months.

Sociodemographic and medical covariates were incorporated into the analysis to assess whether heterogeneity in intercept and slope can be predicted. Results are presented in Table IV. Symptoms presence/severity and psychological variables at baseline were also considered.

Table IV Effect of various covariates (sociodemographics, medical, symptoms, pshychological state at baseline) on the mean trajectory of the various psychological outcomes. Time is treated using incremental values from 0 to 4. The p-value of the effect on intercept and slope are reported. Color density is proportional to significant levels 0.001, 0.01 and 0.05.

	PDS		CESD		CERQ Negative		CERQ Positive		EGO Resilience		PACT Forward focus		PACT Trauma focus	
	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
Participation in the intervention	0.0077	0.0441	0.0345	0.0970	0.0924	0.0425	0.0033	0.0002	0.4921	0.1196	0.0116	0.0101	0.2859	0.2571
Herceptin	0.7053	0.9588	0.8646	0.3551	0.9776	0.4166	0.8101	0.3464	0.7506	0.3049	0.8443	0.0121	0.0995	0.0113
Hormonal	0.3367	0.9469	0.4306	0.2537	0.7575	0.9071	0.9885	0.7380	0.3800	0.8865	0.0572	0.3913	0.4747	0.6244
Urban residence	0.0586	0.7721	0.0661	0.5362	0.7265	0.7992	0.2364	0.6359	0.6610	0.6699	0.2287	0.1966	0.8660	0.6117
Marital status	0.6768	0.5738	0.7597	0.0932	0.1154	0.1256	0.2385	0.0211	0.0631	0.0812	0.6367	0.3543	0.0656	0.7649
Israeli	0.1505	0.0532	0.0243	0.0344	0.1453	0.6772	0.7783	0.0320	0.6275	0.1146	0.5744	0.1216	0.9582	0.8498
Have children	0.4025	0.4601	0.8689	0.7993	0.4738	0.5598	0.3266	0.7598	0.5441	0.7164	0.9173	0.5828	0.3532	0.5322
Income from work	0.0638	0.7839	0.0091	0.5444	0.1664	0.8757	0.1390	0.0824	0.7865	0.4146	0.0658	0.5333	0.4179	0.4580
Income from disability pension	0.0985	0.3718	0.0026	0.3656	0.4686	0.9036	0.8509	0.0814	0.9460	0.0843	0.0391	0.3808	0.8478	0.9159
Income from pension	0.5988	0.4264	0.8286	0.3087	0.6996	0.5335	0.3985	0.1789	0.1126	0.4524	0.8447	0.1761	0.1516	0.4609
Carrier	0.8349	0.2545	0.2413	0.0188	0.2565	0.1585	0.0737	0.3683	0.7870	0.7822	0.2378	0.5550	0.2937	0.5713
Family history	0.7298	0.7976	0.4895	0.6617	0.1797	0.5995	0.9197	0.2195	0.4281	0.9915	0.7616	0.3125	0.7177	0.4654
Age	0.3419	0.2453	0.6211	0.1610	0.5051	0.2273	0.0131	0.2297	0.9854	0.4792	0.9989	0.0612	0.9888	0.0319

	Average Flexibility		Total Flexibility		Functional Impairment		PTG		Resilence Today		Stress Today		Hope Today	
	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
Participation in the intervention	0.0278	0.0232	0.1200	0.0861	0.0281	0.4520	0.8752	0.0238	0.1708	0.1990	0.0122	0.3776	0.5412	0.9673
Herceptin	0.5786	0.0181	0.1144	0.1886	0.6093	0.1306	0.9361	0.0707	0.3145	0.6088	0.9183	0.6125	0.7069	0.3320
Hormonal	0.1054	0.8346	0.1670	0.8890	0.4921	0.6245	0.9567	0.8246	0.2505	0.3600	0.1953	0.8554	0.3224	0.0972
Urban residence	0.4406	0.7294	0.9287	0.9121	0.0514	0.0925	0.8221	0.4091	0.2748	0.7048	0.6049	0.9332	0.6136	0.3069
Marital status	0.2836	0.5376	0.1271	0.3719	0.6553	0.6186	0.8991	0.4363	0.0924	0.2159	0.5212	0.1243	0.0641	0.4396
Israeli	0.7145	0.3024	0.7743	0.3097	0.1656	0.3379	0.8468	0.0993	0.0048	0.6445	0.5863	0.2630	0.2493	0.0236
Have children	0.6516	0.4903	0.6223	0.3856	0.5979	0.5661	0.2568	0.5735	0.7392	0.2090	0.6803	0.2957	0.3601	0.0229
Income from work	0.3640	0.5337	0.7369	0.4880	0.1692	0.9310	0.1800	0.5889	0.2596	0.6302	0.0645	0.6979	0.2855	0.7958
Income from disability pension	0.1392	0.5906	0.3460	0.6892	0.0195	0.7562	0.2220	0.1957	0.1887	0.2439	0.0218	0.5257	0.4097	0.3098
Income from pension	0.4652	0.4143	0.2620	0.6884	0.2214	0.6500	0.1790	0.0546	0.9487	0.2609	0.0766	0.0259	0.4962	0.5261
Carrier	0.2224	0.5694	0.4600	0.4918	0.8135	0.7975	0.6747	0.5405	0.8101	0.2911	0.1097	0.6547	0.5028	0.4567
Family history	0.9468	0.5423	0.6872	0.5815	0.2096	0.6614	0.8292	0.8150	0.0503	0.3766	0.4506	0.8376	0.4043	0.7774
Age	0.9912	0.0197	0.8930	0.0336	0.2494	0.0743	0.0047	0.5418	0.5209	0.8198	0.2671	0.6217	0.4962	0.5599

	PDS		CESD		CERQ Negative		CERQ Positive		EGO Resilience		PACT Forward focus		PACT Trauma focus	
	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
Heat Waves	0.1080	0.6677	0.0764	0.4473	0.5238	0.5356	0.9757	0.6854	0.8561	0.4947	0.5887	0.8896	0.3560	0.5954
Mood Swings	0.0000	0.0210	0.0000	0.0028	0.0168	0.7601	0.4382	0.1755	0.3548	0.2019	0.0009	0.0380	0.0060	0.2742
Sleep Problems	0.0339	0.4579	0.0339	0.7240	0.7785	0.8296	0.7044	0.1229	0.5345	0.9133	0.9123	0.8247	0.6343	0.8209
Obesity	0.2233	0.9966	0.0760	0.3732	0.4905	0.7353	0.5443	0.4253	0.7685	0.6262	0.8073	0.7028	0.3288	0.4601
Decrease in comfort with the body	0.0184	0.9296	0.0003	0.0460	0.2969	0.0199	0.8474	0.3906	0.7998	0.8620	0.0022	0.4785	0.0002	0.0478
Disruption in sexuality	0.0010	0.0412	0.0073	0.0020	0.2135	0.5257	0.6685	0.1372	0.4352	0.7169	0.1917	0.1135	0.3602	0.5107
Inference with a sense of feminity	0.0000	0.3029	0.0000	0.0043	0.2903	0.8747	0.2590	0.8366	0.8602	0.6601	0.0029	0.1560	0.0139	0.6119
Heat Waves: How much	0.0046	0.4013	0.0027	0.9104	0.0422	0.6872	0.3461	0.9687	0.0348	0.6723	0.0858	0.8841	0.0794	0.4576
Mood Swings: How much	0.0000	0.1474	0.0000	0.0021	0.0001	0.6772	0.3763	0.9143	0.6240	0.5134	0.0000	0.7384	0.0101	0.3326
Sleep Problems: How much	0.0000	0.1871	0.0000	0.8956	0.1280	0.9675	0.3705	0.2151	0.0347	0.8909	0.0025	0.3084	0.0323	0.8306
Obesity: How much	0.0249	0.8181	0.0018	0.7648	0.2772	0.9044	0.8970	0.7736	0.5329	0.2911	0.2625	0.8241	0.2276	0.3872
Decrease in comfort with the body: How much	0.0007	0.5314	0.0000	0.0865	0.0672	0.2166	0.6323	0.1937	0.6860	0.2926	0.0021	0.6492	0.0070	0.1920
Disruption in sexuality: How much	0.0000	0.0265	0.0000	0.0017	0.0145	0.7399	0.7927	0.6847	0.8505	0.8552	0.0125	0.0756	0.3349	0.3451
Inference with a sense of feminity: How much	0.0000	0.3146	0.0000	0.0006	0.0145	0.5512	0.1870	0.6686	0.2290	0.9821	0.0000	0.2911	0.0009	0.6041

	Average Flexibility		Total Flexibility		Functional Impairment		PTG		Resilence Today		Stress Today		Hope Today	
	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
Heat Waves	0.4536	0.7658	0.4660	0.7996	0.0827	0.5089	0.3511	0.6494	0.4524	0.9143	0.1363	0.6891	0.6902	0.1833
Mood Swings	0.0005	0.0572	0.0034	0.1138	0.0000	0.3155	0.0032	0.3013	0.0000	0.0161	0.0000	0.0141	0.0032	0.7394
Sleep Problems	0.7880	0.9230	0.5830	0.8286	0.1937	0.4038	0.0004	0.4567	0.4360	0.7351	0.6404	0.7513	0.5707	0.1714
Obesity	0.5644	0.7607	0.3846	0.7879	0.1758	0.6436	0.3556	0.4443	0.2864	0.7482	0.2148	0.0334	0.9690	0.1781
Decrease in comfort with the body	0.0002	0.3116	0.0014	0.3245	0.0004	0.6914	0.0329	0.0323	0.0752	0.8223	0.2244	0.8673	0.2739	0.2131
Disruption in sexuality	0.1952	0.1832	0.2165	0.3118	0.0000	0.0347	0.0057	0.3371	0.4722	0.4239	0.2852	0.9856	0.6207	0.9051
Inference with a sense of feminity	0.0017	0.2332	0.0037	0.1345	0.0000	0.6459	0.0122	0.1447	0.0093	0.1359	0.0341	0.8854	0.0407	0.6725
Heat Waves: How much	0.0546	0.7414	0.0336	0.2985	0.0005	0.2400	0.9862	0.9905	0.1531	0.5627	0.1353	0.4691	0.1523	0.1458
Mood Swings: How much	0.0001	0.7744	0.0007	0.7299	0.0000	0.0149	0.1948	0.5341	0.0000	0.1071	0.0000	0.0199	0.0007	0.6400
Sleep Problems: How much	0.0027	0.4334	0.0024	0.6014	0.0002	0.8261	0.0671	0.0964	0.0006	0.6268	0.0034	0.6703	0.0162	0.0867
Obesity: How much	0.2007	0.9535	0.1877	0.7076	0.0072	0.5926	0.4183	0.6198	0.0697	0.6516	0.0023	0.0820	0.7232	0.0987
Decrease in comfort with the body: How much	0.0011	0.4747	0.0073	0.6362	0.0000	0.5231	0.1128	0.0784	0.0041	0.3336	0.0007	0.6196	0.1632	0.2772
Disruption in sexuality: How much	0.0320	0.1674	0.0884	0.1856	0.0000	0.0236	0.0070	0.2104	0.0467	0.2157	0.0111	0.5399	0.1336	0.8755
Inference with a sense of feminity: How much	0.0000	0.3412	0.0000	0.0881	0.0000	0.4747	0.2174	0.2458	0.0002	0.1057	0.0006	0.5319	0.0009	0.4525

	PDS		CESD		CERQ Negative		CERQ Positive		EGO Resilience		PACT Forward focus		PACT Trauma focus	
	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
Today distress level	0.0000	0.0267	0.0000	0.0032	0.0000	0.1745	0.1146	0.3964	0.0009	0.7036	0.0000	0.1423	0.0009	0.0932
Level of Perceived Resilience Today	0.0000	0.0399	0.0000	0.1535	0.0000	0.3451	0.0147	0.2243	0.0074	0.1853	0.0000	0.9986	0.0003	0.4708
Amount of hope for the future	0.0000	0.0350	0.0000	0.0001	0.0017	0.3306	0.0037	0.7155	0.0005	0.7481	0.0000	0.3542	0.0666	0.5994
PACT Average Flexibility	0.0000	0.0023	0.0000	0.0063	0.0058	0.9974	0.0000	0.1546	0.0000	0.1547	0.0000	0.0000	0.0000	0.0000
PTG Post traumatic growth	0.6098	0.6687	0.2627	0.4599	0.7421	0.7561	0.0000	0.9030	0.0000	0.6495	0.0807	0.1127	0.3456	0.2600
EGO Resilience	0.0005	0.0957	0.0001	0.6342	0.0210	0.6300	0.0000	0.3541	0.0000	0.0000	0.0000	0.0102	0.0000	0.0498
Functional impairment	0.0000	0.0023	0.0000	0.0041	0.0003	0.9466	0.0140	0.6983	0.0007	0.7983	0.0000	0.8358	0.0028	0.0923
CESD Total depression	0.0000	0.0021	0.0000	0.0000	0.0000	0.2847	0.0021	0.7570	0.0000	0.9627	0.0000	0.6174	0.0005	0.0908
CERQ Positive	0.0495	0.0689	0.0182	0.2952	0.6050	0.8734	0.0000	0.0000	0.0000	0.0016	0.0000	0.0047	0.0000	0.6889
CERQ Negative	0.0000	0.1160	0.0000	0.2673	0.0000	0.0000	0.5998	0.1907	0.0398	0.6628	0.0003	0.4138	0.9849	0.7316
PDS Post traumatic stress symptoms	0.0000	0.0000	0.0000	0.0003	0.0000	0.9012	0.0510	0.8156	0.0008	0.8274	0.0000	0.2357	0.0035	0.2943
PACT Forward Focus	0.0000	0.0009	0.0000	0.0283	0.0004	0.8541	0.0000	0.7760	0.0000	0.1892	0.0000	0.0000	0.0000	0.0017
PACT Trauma Focus	0.0119	0.6792	0.0032	0.3365	0.8993	0.3059	0.0006	0.8498	0.0000	0.0918	0.0000	0.0002	0.0000	0.0000
PACT Total Coping	0.0000	0.0409	0.0000	0.0779	0.0411	0.7677	0.0000	0.9657	0.0000	0.0769	0.0000	0.0000	0.0000	0.0000
PACT Polarity	0.3465	0.8211	0.3752	0.9428	0.3180	0.5193	0.0363	0.5584	0.0056	0.3828	0.2793	0.0006	0.0000	0.0114
PACT Discrepancy	0.0000	0.0018	0.0000	0.1036	0.0000	0.0976	0.1542	0.3714	0.1488	0.6507	0.0000	0.0001	0.0000	0.0017
PACT Total Flexibility	0.0000	0.0647	0.0000	0.1136	0.1259	0.7496	0.0000	0.9492	0.0000	0.0692	0.0000	0.0000	0.0000	0.0000
PTG I Relating to Others	0.8589	0.5032	0.0865	0.2143	0.3673	0.8455	0.0003	0.9449	0.0001	0.9347	0.0835	0.1326	0.3870	0.1529
PTG II – New Possibilities	0.8457	0.6073	0.3059	0.7123	0.7113	0.5667	0.0000	0.6290	0.0000	0.4669	0.1450	0.0815	0.5394	0.1678
PTG III – Personal Strength	0.7807	0.5377	0.2530	0.5014	0.9465	0.7325	0.0000	0.4799	0.0000	0.5592	0.0035	0.1204	0.0554	0.7626
PTG IV - Spiritual Change	0.3233	0.8862	0.6128	0.4087	0.2976	0.4457	0.0602	0.2885	0.0007	0.6468	0.5029	0.1999	0.8987	0.3315
PTG V - Appreciation of Life	0.0631	0.9585	0.8329	0.9472	0.2512	0.9018	0.0001	0.4330	0.0047	0.5452	0.7127	0.1952	0.7534	0.4404
PTG SF I Relating to Others	0.2534	0.3091	0.0271	0.2278	0.6657	0.4760	0.0000	0.9352	0.0008	0.7412	0.0242	0.1419	0.0150	0.5224
PTG SF II New Possibilities	0.4992	0.1645	0.1287	0.1580	0.5781	0.5907	0.0000	0.7081	0.0000	0.2258	0.1610	0.0572	0.5909	0.0144
PTG SF III Personal Strength	0.8091	0.3223	0.5018	0.8444	0.8768	0.6555	0.0000	0.3025	0.0001	0.7633	0.0020	0.1641	0.0264	0.8675
PTG SF IV Spiritual Change	0.3233	0.8862	0.6128	0.4087	0.2976	0.4457	0.0602	0.2885	0.0007	0.6468	0.5029	0.1999	0.8987	0.3315
PTG SF V Appreciation of Life	0.0058	0.8694	0.2186	0.6447	0.2315	0.8271	0.0028	0.4642	0.0291	0.4400	0.3603	0.1881	0.7589	0.3434
PTG SF (Short Form)	0.5485	0.6182	0.3856	0.4477	0.9952	0.8620	0.0000	0.8066	0.0000	0.4630	0.1067	0.0856	0.3127	0.2383
CESD I - Depressed affect	0.0000	0.0016	0.0000	0.0000	0.0000	0.2813	0.0088	0.5741	0.0011	0.9896	0.0000	0.4772	0.0046	0.2291
CESD II– Positive affect	0.0000	0.0099	0.0000	0.0000	0.0046	0.6654	0.0000	0.3979	0.0000	0.7215	0.0000	0.2804	0.0001	0.1164
CESD III – Somatic symptoms	0.0000	0.0509	0.0000	0.0003	0.0000	0.5261	0.0875	0.4498	0.0022	0.7107	0.0000	0.7801	0.0027	0.2403
CESD IV – Interpersonal	0.0000	0.0001	0.0000	0.5295	0.0000	0.0077	0.3336	0.2776	0.0024	0.4851	0.0000	0.2948	0.7310	0.0344
PDS Re-experiencing	0.0000	0.0000	0.0000	0.0001	0.0000	0.9142	0.0843	0.9665	0.0021	0.5874	0.0000	0.3459	0.0064	0.5575
PDS Avoidance	0.0000	0.0000	0.0000	0.0009	0.0000	0.6083	0.0047	0.6167	0.0001	0.5658	0.0000	0.3173	0.0010	0.2674
PDS Arousal	0.0000	0.0000	0.0000	0.0263	0.0001	0.8554	0.6330	0.7008	0.0935	0.8756	0.0000	0.2497	0.1211	0.3808

	Average Flexibility		Total Flexibility		Functional		PTG		Resilence Today		Stress Today		Hope Today	
	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
Today distress level	0.0000	0.1389	0.0000	0.2281	0.0000	0.1127	0.3628	0.2900	0.0000	0.0201	0.0000	0.0000	0.0000	0.2657
Level of Perceived Resilience Today	0.0000	0.8931	0.0000	0.9445	0.0000	0.3005	0.2708	0.8597	0.0000	0.0000	0.0000	0.0003	0.0000	0.0148
Amount of hope for the future	0.0000	0.8609	0.0000	0.7345	0.0000	0.0582	0.0651	0.7067	0.0000	0.0007	0.0000	0.0046	0.0000	0.0000
PACT Average Flexibility	0.0000	0.0000	0.0000	0.0000	0.0000	0.0736	0.0756	0.5148	0.0000	0.7335	0.0000	0.0528	0.0000	0.2276
PTG Post traumatic growth	0.1062	0.1127	0.0767	0.3163	0.5166	0.0787	0.0000	0.0000	0.2438	0.5081	0.2321	0.3460	0.0085	0.9023
EGO Resilience	0.0000	0.0059	0.0000	0.0795	0.0005	0.1152	0.0000	0.8353	0.0213	0.2321	0.0024	0.1646	0.0012	0.6823
Functional impairment	0.0000	0.4493	0.0000	0.7191	0.0000	0.0000	0.5762	0.6017	0.0000	0.6536	0.0000	0.4605	0.0000	0.0564
CESD Total depression	0.0000	0.4316	0.0000	0.8094	0.0000	0.0290	0.2028	0.7737	0.0000	0.0660	0.0000	0.0027	0.0000	0.5973
CERQ Positive	0.0000	0.0400	0.0000	0.2809	0.0132	0.0910	0.0000	0.0166	0.0381	0.3321	0.1615	0.0798	0.0025	0.5018
CERQ Negative	0.0133	0.4823	0.1228	0.4933	0.0005	0.4771	0.8041	0.6790	0.0001	0.3958	0.0000	0.3342	0.0021	0.2194
PDS Post traumatic stress symptoms	0.0000	0.6244	0.0000	0.8591	0.0000	0.0008	0.5527	0.5218	0.0000	0.2930	0.0000	0.0079	0.0000	0.3441
PACT Forward Focus	0.0000	0.0000	0.0000	0.0000	0.0000	0.0278	0.1230	0.3787	0.0000	0.6987	0.0000	0.0035	0.0000	0.3239
PACT Trauma Focus	0.0000	0.0000	0.0000	0.0000	0.0111	0.8422	0.4017	0.4469	0.0002	0.8263	0.0024	0.4454	0.0739	0.2536
PACT Total Coping	0.0000	0.0000	0.0000	0.0000	0.0000	0.2060	0.1867	0.3901	0.0000	0.6628	0.0000	0.0259	0.0000	0.3375
PACT Polarity	0.0025	0.0018	0.0000	0.0001	0.3257	0.9772	0.1201	0.9467	0.1265	0.1266	0.4839	0.9248	0.0467	0.0715
PACT Discrepancy	0.0105	0.1276	0.9877	0.2071	0.0001	0.0136	0.3269	0.4005	0.0119	0.9488	0.0003	0.0695	0.0000	0.1891
PACT Total Flexibility	0.0000	0.0000	0.0000	0.0000	0.0000	0.2883	0.1040	0.4545	0.0000	0.4879	0.0000	0.1115	0.0000	0.1926
PTG I Relating to Others	0.1164	0.0915	0.0639	0.3498	0.4384	0.1302	0.0000	0.0000	0.0258	0.5329	0.1757	0.2826	0.0006	0.6826
PTG II – New Possibilities	0.2025	0.0674	0.1621	0.2041	0.2274	0.0351	0.0000	0.0000	0.3526	0.4622	0.2267	0.3652	0.0161	0.9836
PTG III – Personal Strength	0.0045	0.2548	0.0034	0.3174	0.4361	0.1123	0.0000	0.0000	0.4040	0.6459	0.1721	0.5815	0.0330	0.8512
PTG IV - Spiritual Change	0.5990	0.1830	0.5467	0.4190	0.8279	0.2430	0.0000	0.0004	0.4909	0.3395	0.5744	0.6269	0.0820	0.7937
PTG V - Appreciation of Life	0.6919	0.2326	0.7046	0.3653	0.6515	0.4685	0.0000	0.0000	0.6317	0.4369	0.7880	0.3459	0.3743	0.6847
PTG SF I Relating to Others	0.0095	0.1735	0.0022	0.5746	0.0798	0.1204	0.0000	0.0003	0.0484	0.5866	0.4247	0.4679	0.0071	0.6261
PTG SF II New Possibilities	0.2297	0.0169	0.1607	0.0268	0.0868	0.0171	0.0000	0.0000	0.3464	0.2689	0.1136	0.1106	0.0051	0.9123
PTG SF III Personal Strength	0.0020	0.3083	0.0008	0.3556	0.6979	0.1833	0.0000	0.0000	0.4446	0.8640	0.6064	0.4987	0.0822	0.7475
PTG SF IV Spiritual Change	0.5990	0.1830	0.5467	0.4190	0.8279	0.2430	0.0000	0.0004	0.4909	0.3395	0.5744	0.6269	0.0820	0.7937
PTG SF V Appreciation of Life	0.4500	0.1934	0.5037	0.2767	0.1406	0.9448	0.0000	0.0000	0.0902	0.4822	0.5161	0.6355	0.9964	0.6252
PTG SF (Short Form)	0.0991	0.0849	0.0558	0.2470	0.6285	0.0944	0.0000	0.0000	0.5366	0.5070	0.4973	0.4643	0.0250	0.7840
CESD I - Depressed affect	0.0000	0.6623	0.0000	0.9851	0.0000	0.0128	0.2683	0.9194	0.0000	0.1182	0.0000	0.0006	0.0000	0.3738
CESD II– Positive affect	0.0000	0.1320	0.0000	0.3423	0.0000	0.3297	0.0404	0.6163	0.0000	0.0594	0.0000	0.0778	0.0000	0.2998
CESD III – Somatic symptoms	0.0000	0.6858	0.0000	0.9448	0.0000	0.0522	0.7403	0.6105	0.0000	0.0859	0.0000	0.0261	0.0000	0.3868
CESD IV – Interpersonal	0.0034	0.1003	0.0190	0.1150	0.0000	0.1844	0.1134	0.4608	0.0003	0.2086	0.0009	0.0339	0.0001	0.3748
PDS Re-experiencing	0.0000	0.8036	0.0000	0.8642	0.0000	0.0006	0.8718	0.6414	0.0000	0.0979	0.0000	0.0002	0.0000	0.1913
PDS Avoidance	0.0000	0.5590	0.0000	0.8158	0.0000	0.0009	0.9756	0.2961	0.0000	0.1471	0.0000	0.1210	0.0000	0.6761
PDS Arousal	0.0000	0.6388	0.0009	0.9088	0.0000	0.0157	0.1565	0.8809	0.0000	0.6842	0.0000	0.0663	0.0022	0.2082

6.4.2 HUS dataset

Analysis plan

A mixed-effects linear regression analysis was performed in order to analyze the change over time of the various QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scales over the 3-year observation period. The assessment of the effect of sociodemographic, medical variables and reported

symptoms at baseline on the average trajectory of the previously mentioned psychological measures is work in progress. The analysis was performed using lcmm package in R.

Results

Table V depicts for which scales the rate of change (slope) is statistically different from zero. It is noted that the slope is small in most cases. The regression lines that approximates the average trajectory for indicative psychological outcomes are depicted in Figure 23.

Table V Results of the mixed-effects linear regression model for each psychological outcome with only time as a regressor. Time is treated using incremental values from 0 to 4. The estimated regression coefficient of the slope and the p-value of the Wald test are reported. Color density is proportional to significant levels 0.01 and 0.05.

	Intercept	Slope: linear term	Slope: quadratic term	Wald test for slope: p-value
C30 Global QoL	70.8	1.330	-0.162	0.0016
C30 Physical functioning	82.6	1.052	-0.107	0.0000
C30 Role functioning	87.1	0.873	-0.091	0.0463
C30 Emotional functioning	81.6	0.806	-0.091	0.0454
C30 Cognitive functioning	84.5	0.002	0.008	0.8273
C30 Social functioning	87.9	2.353	-0.251	0.0000
C30 Fatigue	27.6	-1.675	0.180	0.0000
C30 Nausea and vomiting	3.1	-0.420	0.050	0.1379
C30 Pain	17.8	1.026	-0.111	0.0301
C30 Dyspnea	7.0	-0.227	0.016	0.4059
C30 Insomnia	31.5	-2.189	0.242	0.0003
C30 Appetite loss	4.9	-1.296	0.178	0.0002
C30 Constipation	10.5	0.401	-0.055	0.5816
C30 Diarrhea	6.3	-0.398	0.068	0.2452
C30 Financial impact	11.1	-2.054	0.181	0.0000
BR23 Body image	64.5	4.192	-0.361	0.0000
BR23 Sexual functioning	30.2	1.587	-0.251	0.0001
BR23 Sexual enjoyment	59.4	0.553	-0.132	0.0407
BR23 Future perspective	55.3	3.252	-0.200	0.0000
BR23 Systemic therapy side effects	21.2	-1.765	0.160	0.0000
BR23 Breast symptoms	19.0	-2.538	0.163	0.0000
BR23 Arm symptoms	19.2	-0.064	-0.083	0.0000
BR23 Upset by hair loss	32.1	-11.145	1.067	0.0000
WHQ Depressed mood	0.8	0.007	-0.001	0.2481
WHQ Somatic symptoms	0.7	-0.002	0.001	0.3910
WHQ Memory/concentration	0.6	-0.003	0.001	0.0263
WHQ Vasomotor Symptoms	0.3	0.014	0.001	0.0000
WHQ Anxiety/fears	0.9	0.001	0.000	0.3027
WHQ Sexual behaviour	0.6	0.006	-0.001	0.3162
WHQ Sleep Problems	0.6	0.015	-0.001	0.0048
WHQ Menstrual symptoms	0.7	0.017	-0.001	0.0000
WHQ Attractiveness	0.7	0.019	-0.003	0.0126
BDI Depression	3.8	-0.287	0.030	0.0001
FACIT – F score	40.9	0.8027	-0.08832	0.0000

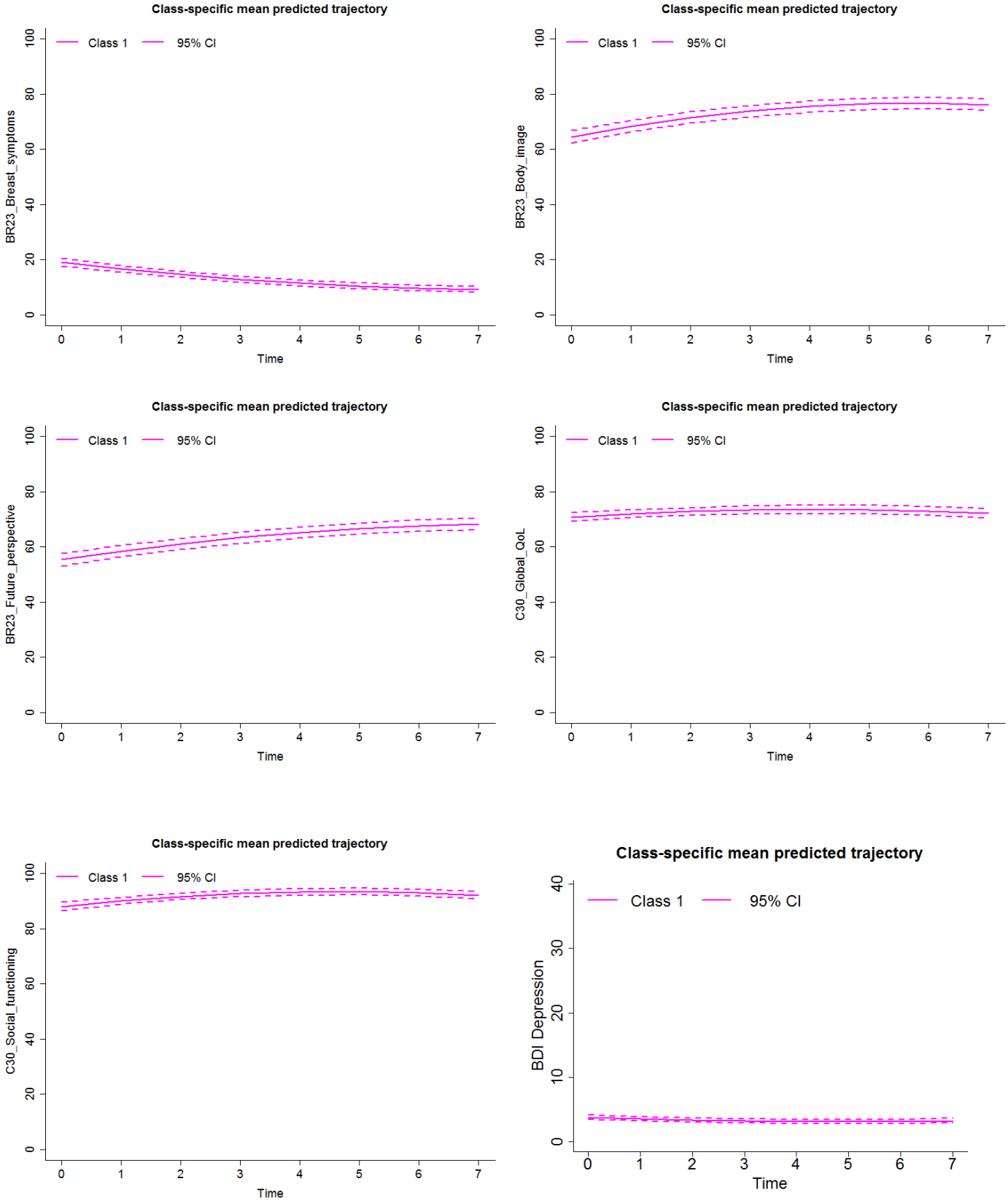

Figure 23. Mean predicted trajectories for indicative psychological outcomes. Coding: Time 0: baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 18 months; Time 5: 24 months; Time 6: 30 months; Time 7: 36 months.

6.4.3 Subjective criteria-based trajectory analysis: HUJI dataset

Analysis plan

The individual trajectories of psychological outcomes CERQ, PACT, PTGI, EGO, CES-D, PDS, functional impairment and the levels of distress, hope and resilience throughout a two year observation period were analyzed. Assignment rules based on subjective categorization criteria to construct categories of growth trajectories was considered as described below per psychological scale.

Results

PDS Trajectory

The individual trajectories of posttraumatic stress symptoms over a two year period have been analyzed and patients have been classified, based on their initial PDS value and the fluctuation of PDS values at Months 3, 6, 12 and 24 from baseline. The overall, average PDS severity score in the HUJI dataset ranges between 0-3, which is obtained by adding up the individual's responses of the 17 symptom items and then by dividing with the number of the items. We have considered the following cut offs for the average symptom severity rating based on literature search (Table I): 0-0.59 low/mild, 0.64-1.17 moderate, 1.23-2.06 moderate to severe, and >2.1 severe. Furthermore, if the change in the average PDS value between two time points is equal or less than 0.35 (equals to a change of 6 points in sum score), then the PDS is considered to remain stable. This value corresponds to 12% of the whole value range. We also examine whether fluctuation expands within or between two or more severity categories as defined by the previously reported cut offs. Based on the above criteria we can identify the following groups of trajectories:

Table VI Trajectory analysis of posttraumatic stress symptoms based on subjective criteria

PDS value at baseline	Trajectory based on score change	Trajectory based on change in severity category	Number of patients	Comment
Mild	Stable	Stable	40	
	Stable	Increases to moderate	2	
	Improving	Stable	2	
	Increasing	Stable	3	
	Increasing	Increases to moderate	7	
Moderate	Improving	Improves to mild	12	
	Stable	Improves to mild	7	2 have a transient increase
	Stable	Stable	18	5 have a transient increase 2 have a transient improvement
	Increase	Increases to moderate/severe	3	

Moderate to severe	Improving	Improves to mild (6) Improves to moderate (4)	10	
	Improving	Stable	5	3 have a transient improvement
	Stable	Stable	9	2 have transient improvement
	Stable	Increases to severe	1	
	Stable	Improves to moderate	3	
	Increasing	Increases to severe (2) Stable (1)	3	
Severe	Stable	Stable	1	
	Decline	Improves to moderate (1) Improves to moderate/ severe (2)	3	

- 42% of the patients experience mild levels of posttraumatic stress symptoms at baseline (on average 16 months after diagnosis). For the vast majority of these patients (87%), stress symptoms will remain stable over the next two years or will fluctuate within low levels. For the rest stress symptoms will increase to moderate levels.
- 31% of the patients experience moderate levels of posttraumatic stress symptoms at baseline. Symptoms get worst for only a minority of these patients (7.5%), whereas for 30% the symptoms improve to mild levels.
- 24% had moderate to severe posttraumatic stress symptoms at baseline. Symptoms improved for half of them, however, depending on the initial value and the degree of improvement, the severity of stress symptoms may have stayed in moderate to severe levels, declines to moderate or declined to mild levels. Approximately 10% showed increase in stress symptoms.
- Very few patients had severe levels of posttraumatic stress symptoms at baseline, which improved in most cases. It is noted that most of the patients with improvement discontinued the study after six months, hence the trajectory is not complete.

Overall, the majority of patients (62%) are characterized by fairly constant trajectories, 25% by decreasing and 12% by increasing.

Functional impairment

The overall, average functional impairment (FUNCT) score in the HUJI dataset ranges between 0-5, which is obtained by adding up the individual's responses of the 9 symptom items and then by dividing with the number of the items. Since no cut offs exist in literature, we divided the data based on the three quartiles as following: 0 no, 0.111-0.667 low, 0.667-1.778 moderate, >1778 high. Furthermore, if the change in the average FUNCT value between two time points is equal or less than 0.381 (equals to a change of 4 points in sum score), then the PDS is considered to remain stable. This value corresponds to 9% of the whole value range. We also examine whether

fluctuation expands within or between two or more impairment categories as previously defined. Based on the above criteria we can identify the following groups of trajectories:

Table VII Trajectory analysis of functional impairment based on subjective criteria

FUNCT value at baseline	Trajectory based on score change	Trajectory based on change in severity category	Number of patients	Comment
No	Stable	Stable (23) Increase to low (11)	34	Transient increase to low (7) or moderate (3) levels
	Increasing	Increase to low(1) Increase to moderate(5) Increase to high (3)	9	
Low 0.111-0.667	Improving	Improve to No	2	1 has a transient increase to moderate
	Stable	Improve to No (11) Stable (5) Increase to moderate	17	4 have transient increase to moderate 1 has a transient increase to high
	Increasing	Increase to moderate	4	1 has irregular shape
Moderate 0.778-1.778	Improving	Improvement to no (3) Improvement to moderate (8) Stable (1)	12	1 transient improvement to no 4 have transient increase to high
	Stable	Stable(11) Increase to high (1)	12	2 have transient decrease 1 has transient increase 1 has irregular shape
	Increasing	Stable (1) Increase to high (6)	7	1 transient increase 1 transient drop 1 irregular shape
High 1.889-5	Improving	Stable (3) Improve to moderate(9) Improve to low/no (5)	17	3 have irregular shape 1 has a transient improvement
	Stable	Stable	10	2 have transient improvement to moderate 1 has irregular shape
	Increasing	Stable	5	

- 33% of the patients experience no functional impairment at baseline. For the vast majority of these patients (81.5%), functional impairment will remain stable over the next two years or will fluctuate within low levels. For the rest stress symptoms will increase to moderate or high levels.
- 23% of the patients experience low levels of functional impairment at baseline. Functional impairment gets worst for 17% of these patients, whereas for the majority (74%) the functional impairment was stable.
- 24% of the patients experience moderate levels of functional impairment at baseline, based on the considered cut offs. FUNCT gets worst for 23%, whereas for 34% the functional impairment improves.
- 20% had high functional impairment at baseline. Functional impairment improved for half of them (53%), however, depending on the initial value and the degree of improvement, functional impairment may stay high, decline to moderate or decline to low/no levels. Approximately 16% showed an increase in functional impairment.

Overall, the majority of patients (57%) are characterized by constant trajectories, 19% by increasing and 24% by decreasing.

Stress Today

The current self-report distress levels (STRESS) in HUJI dataset ranges between 0-10. We considered a cut off analogous with the one considered for distress thermometer (Cutillo et. al, 2017): 0-3 low, >3 high. Furthermore, if the change in the STRESS value between two time points is equal or less than 1, then STRESS is considered to remain stable. This value corresponds to 10% of the whole value range. We also examine whether fluctuation expands within or between two or more impairment categories as previously defined. Based on the above criteria we can identify the following groups of trajectories:

Table VIII Trajectory analysis of distress levels based on subjective criteria

STRESS value at baseline	Trajectory based on score change	Trajectory based on change in severity category	Number of patients	Comment
Low	Stable	Stable	54	6 have a transient increase 3 have irregular shape
	Increasing	Stable (4) Increase to high (11)	15	2 have a transient increase 1 has irregular shape
	Decline	Stable	6	2 have a transient increase
High	Stable	Stable	15	1 has a transient drop 2 have irregular shapes
	Increasing	Stable	2	1 has a transient drop
	Decline	Decline to low (26) Stable (5)	31	3 have a transient increase 4 have irregular shapes

				1 has transient drop

- The majority of patients (61%) had overall distress levels at baseline below the considered cut-off. For the vast majority of these patients (85%), distress levels will remain stable over the next two years or will fluctuate below the considered cut off. For the rest, distress score increased above cut off.
- Among patients with distress levels above cut-off at baseline, 31% had approximately stable distress levels over the next two years, for 4% distress increased and 65 % had decreasing distress levels.

Overall, approximately half of the patients (56%) are characterized by fairly constant trajectories, 30% by decreasing and 14% by increasing.

Posttraumatic growth

The overall, average score of posttraumatic growth (PTG) in the HUJI dataset ranges between 0-5, which is obtained by adding up the individual's responses of the 21 symptom items and then by dividing with the number of the items. Since no cut offs exist in literature, we dichotomized the data based on the median value: 0-3.381 low, >0.381 high. Furthermore, if the change in the average FUNCT value between two time points is equal or less than 0.38 (equals to a change of 8 points in sum score), then the PTG is considered to remain stable. This value corresponds to 8% of the whole value range. We also examine whether fluctuation expands within or between two or more impairment categories as previously defined. Based on the above criteria we can identify the following groups of trajectories:

Table IX Trajectory analysis of posttraumatic growth based on subjective criteria

PTG value at baseline	Trajectory based on score change	Trajectory based on change in severity category	Number of patients	Comment
Low	Stable	Stable (20) Increase to high (7)	27	4 transient increase
	Increasing	Stable (16) Increase to high (15)	31	
	Decline	Stable	7	
High	Stable	Stable (35) Decline to low (1)	36	2 transient increase 2 transient decline
	Increasing	Stable(11)	11	
	Decline	Decline to low (12) Stable (4)	16	

Few patients (11%) had levels of posttraumatic growth below 2.

- Among patients with posttraumatic growth below median at baseline, 42% had approximately stable PTG levels over the next two years, for 47% PTG increased and only 11 % reported decreasing levels of PTG.
- Among patients with posttraumatic growth above median at baseline, the majority (57%) had approximately stable PTG levels over the next two years, for 18% PTG increased and only 25 % had decreasing levels of PTG.

Overall, half of the patients (49%) are characterized by fairly constant trajectories, 18% by decreasing and 33% by increasing.

Negative cognitive emotional regulation

The overall, average score of negative cognitive emotional regulation (negative CERQ) in the HUJI dataset ranges between 1-5, which is obtained by adding up the individual's responses of the 8 items and then by dividing with the number of the items. Since no cut offs exist in literature, we dichotomized the data based on the median value: 0-2.125 low, >2.125 high. Furthermore, if the change in the average negative CERQ value between two time points is equal or less than 0.5 (equals to a change of 4 points in sum score), then the negative CERQ is considered to remain stable. This value corresponds to 10% of the whole value range. We also examine whether fluctuation expands within or between two or more impairment categories as previously defined. Based on the above criteria we can identify the following groups of trajectories:

Table X Trajectory analysis of negative cognitive emotional regulation based on subjective criteria

negative CERQ value at baseline	**Trajectory based on score change**	**Trajectory based on change in severity category**	**Number of patients**	**Comment**
Low	Stable	Stable (39) Increase to high (8)	47	5 have a transient increase 1 has a transient decline
	Increasing	Stable (1) Increase to high (9)	10	
	Decline	Stable	8	1 has transient increase The decline is small
High	Stable	Stable (25) Decline to low (3)	28	
	Increasing	Stable	6	
	Decline	Decline to low (21) Stable (8)	29	

- Very few patients (5.5%) had levels of negative CERQ above 3.5.
- Among patients with negative CERQ below median at baseline, the majority (72.3%) had approximately stable negative CERQ over the next two years, for 15.4% negative CERQ increased and 12.3% had decreasing levels of negative CERQ.

- Among patients with posttraumatic growth above median at baseline, 44% had approximately stable negative CERQ levels over the next two years, for 10% negative CERQ increased and only 4 % had decreasing levels of negative CERQ.

Overall, approximately half of the patients (59%) are characterized by fairly constant trajectories, 29% by decreasing and 12% by increasing.

Positive cognitive emotional regulation

The overall, average score of positive cognitive emotional regulation (positive CERQ) in the HUJI dataset ranges between 1-5, which is obtained by adding up the individual's responses of the 10 items and then by dividing with the number of the items. Since no cut offs exist in literature, we dichotomized the data based on the median value: 0-3.3 low, >3.3 high. Furthermore, if the change in the average positive CERQ value between two time points is equal or less than 0.5 (equals to a change of 5 points in sum score), then the positive CERQ is considered to remain stable. This value corresponds to 10% of the whole value range. We also examine whether fluctuation expands within or between two or more impairment categories as previously defined. Based on the above criteria we can identify the following groups of trajectories:

Table XI Trajectory analysis of positive cognitive emotional regulation based on subjective criteria

positive CERQ value at baseline	Trajectory based on score change	Trajectory based on change in severity category	Number of patients	Comment
Low	Stable	Stable (23) Increase to high (3)	26	4 have a transient increase 1 has a transient decline
	Increasing	Stable (6) Increase to high (25)	31	2 have a transient increase 4 have irregular shapes
	Decline	Stable	8	1 has transient increase
High	Stable	Stable (37) Decline to low (3)	40	4 have transient decline 3 have transient increase 1 has irregular shape
	Increasing	Stable	4	1 has a transient drop
	Decline	Decline to low (14) Stable (4)	18	2 have irregular shapes 1 has a transient decline

- Very few patients (3.6%) had levels of positive CERQ below 2.
- Among patients with positive CERQ below median at baseline, the 40% had approximately stable positive CERQ over the next two years, for 48% positive CERQ increased and 12.3% had decreasing levels of positive CERQ.
- Among patients with posttraumatic growth above median at baseline, 64.5% had approximately stable positive CERQ levels over the next two years, for 6.5% positive CERQ increased and only 29 % haddecreasing levels of positive CERQ.

Overall, approximately half of the patients (52%) are characterized by fairly constant trajectories, 20% by decreasing and 28% by increasing.

Depression

The overall, average score of CES-D questionnaire in the HUJI dataset ranges between 0-3, which is obtained by adding up the individual's responses of the 20 items and then by dividing with the number of the items. We have considered the following cut offs for the average symptom severity rating based on literature search (Table I): 0-0.8 not depressed, >=0.08 depressed. Furthermore, if the change in the average CES-D value between two time points is equal or less than 0.3 (equals to a change of 6 points in sum score), then the PTG is considered to remain stable. This value corresponds to 10% of the whole value range. We also examine whether fluctuation expands within or between two or more impairment categories as previously defined. Based on the above criteria we can identify the following groups of trajectories:

Table XII Trajectory analysis of depression based on subjective criteria

CES-D value at baseline	Trajectory based on score change	Trajectory based on change in severity category	Number of patients	Comment
Not depressed	Stable	Stable (61) Increase to depressed (2)	63	5 have a transient increase
	Increasing	Stable (5) Increase to depressed (8)	13	
	Decline	Stable	7	
Depressed	Stable	Stable (14) Decline to not depressed (1)	15	3 have a transient increase
	Increasing	Stable	6	
	Decline	Decline to not depressed (14) Stable (11)	25	

- The majority of patients (64%) had levels of CES-D below the cut-off for depression at baseline. For the vast majority of these patients (90%), CES-D score remained stable over the next two years or fluctuated below the cut off for depression. For the rest CES-D score increased to depressed levels.
- Among patients with CES-D above cut-off at baseline, 33% had approximately stable CES-D levels over the next two years, for 13% CES-D increased and 54 % had decreasing levels of CES-D.

Overall, approximately half of the patients (60%) are characterized by fairly constant trajectories, 25% by decreasing and 15% by increasing.

Flexibility

The overall score of total flexibility (FLEX) as defined in Bonnano et al (2011) has been calculated based on PACT scores in HUJI dataset. Since no cut offs exist in literature, we dichotomized the data based on the median value: 0-10 low, >10 high. Furthermore, if the change in the average FLEX value between two time points is equal or less than 1.4, then the FLEX score is considered to remain stable. This value corresponds to 10% of the whole value range. We also examine whether fluctuation expands within or between two or more impairment categories as previously defined. Based on the above criteria we can identify the following groups of trajectories:

Table XIII Trajectory analysis of total flexibility based on subjective criteria

FLEX value at baseline	Trajectory based on score change	Trajectory based on change in severity category	Number of patients
Low	Stable	Stable (29) Increase to high (1)	30
	Increasing	Stable (12) Increase to high (17)	29
	Decline	Stable	10
High	Stable	Stable (35) Decline to low (3)	38
	Increasing	Stable(5)	5
	Decline	Decline to low (10) Stable (6)	16

- Very few patients (5%) had scores of FLEX below 5 at baseline (value range 2-14).
- Among patients with FLEX below median at baseline, 43% had approximately stable FLEX scores over the next two years, for 42% PTG increased and only 15 % had decreasing levels of FLEX.
- Among patients with FLEX scores above median at baseline, the majority (64%) had approximately stable FLEX levels over the next two years, for 8% PTG increased and only 27 % had decreasing levels of FLEX.

Overall, half of the patients (53%) of the patients are characterized by fairly constant trajectories, 20% by decreasing and 27% by increasing.

6.5 Latent-class mixed-effects analysis

6.5.1 The HUJI dataset

Analysis plan

A latent-class mixed-effects regression analysis was performed in order to identify sub-groups of patients with distinct trajectory patterns of the psychological variables. The analysis was performed using the lcmm package of R. A linear and a quadratic model of the change across time was considered. Models with one to five latent growth classes were fit to the data. Each model was run several times from different sets of initial values (typically from a grid of initial values) to avoid convergence to local minima. The number of latent growth classes that best fit the data were assessed by identifying the model with the lowest AIC. Furthermore, the minimal class size should be at least 6% of patients and the average posterior probability of class membership should be above 0.7.

After identifying the latent class solution that best fit the data, differences among the predicted classes were examined for important covariates and concurrent outcomes outside the models. Analyses of variance (ANOVA) and chi-squared analyses were used to assess for differences in demographic and clinical characteristics, symptom severity scores and other psychological outcomes of interest at baseline among the GMM latent classes. Alternative approaches (consideration of covariates in class membership and/or mixture model, multivariate modelling, consideration of alternative link functions) is work in progress. Indicative results are presented below for CES-D, PDS, and functional impairment.

PDS Trajectories

A logit transformation was also applied, as many PDS observations were close to the boundaries. However, BIC and AIC values were not improved and the relevant models were not selected for further analysis.

In terms of AIC, the optimal model that described post-traumatic stress symptoms was the quadratic one with four classes. However, the lowest BIC value had the linear two-class model. Taking into consideration the variability of trajectories that characterize the PDS as previously described, the quadratic four-class solution was adopted for further examination. Figure 24 shows the resulting trajectories for the four-group model and the actual measurements of the patients that compose each class. The most frequent class (68.2% - labeled class 2) has relatively stable levels of low or moderate post-traumatic stress symptoms across assessment points. The second largest class (14.7% - labeled class 4) was composed of participants with high levels of PDS (either stable or increasing at each measurement). The two remaining classes evidenced different quadratic patterns indicative of recovery. One class (10.9 % - labeled class 1) had elevated stress symptoms at baseline, but gradually declined and for some patients reach low levels after two years. The remaining class and also the least frequent (6.2% - labeled class 3) showed a reverse quadratic pattern of low to moderate stress symptoms at baseline, then elevated stress symptom at six to twelve months after baseline, followed by low stress months after two years.

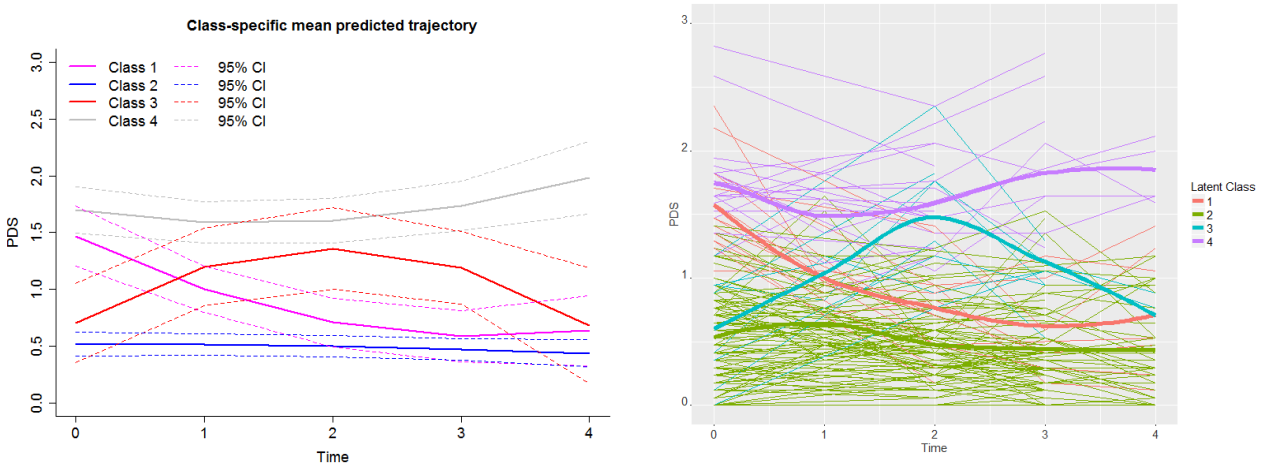

Figure 24. Mean predicted posttraumatic stress symptoms trajectories and spaghetti plot (each thin line connects the responses for the same patient over time) with the mean PDS score at each measurement point for the four classes identified by the latent class model. Coding: Time 0:baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 24 months.

Functional Impairment Trajectories

For functional impairment, the best fitting unconditional model was the quadratic one with three classes. Figure 25 shows the resulting trajectories from for the three-group model and the actual measurements of the patients that compose each class. The majority of patients (62.8%) were assigned to a class (labeled class 2) with relatively stable levels of low functional impairment across assessment points. The second largest class (24.8%-labeled class 1) was composed primarily of participants with moderate levels of functional impairment that slightly decline over the two year period. The final and least frequent class (12.4% - labeled class 3) had elevated functional impairment across assessment points.

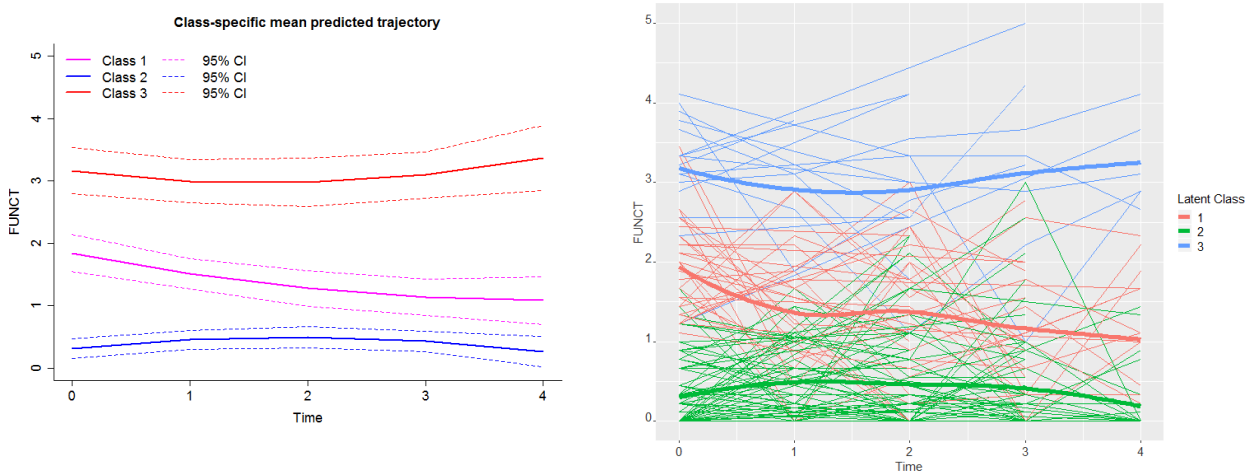

Figure 25. Mean predicted functional impairment trajectories and spaghetti plot (each thin line connects the responses for the same patient over time) with the mean score at each measurement point for the three classes identified by the latent class model. Coding: Time 0:baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 24 months.

CES-D Trajectories

For depression, the model that best described the data was the quadratic one with four latent classes. Figure 26 shows the resulting trajectories from for the four-group model and the actual

measurements of the patients that compose each class. No covariates other than time in the specification of the trajectories and no predictors of trajectory group membership are considered.

The largest trajectory group accounted for 65% of the patients (labeled class 3) and was composed of patients who generally had relatively low levels of depression throughout the two-year period. The trajectory labeled class 1, estimated to account for 7.8% of the patients, reported initial high CES-D levels that remained high over the two years. The group labeled class 4, accounting for 15.5% of the patients, began with relatively high levels of depression which subsequently declined and the final group, labeled class 2 and accounting for 11.6% of the population, had relatively moderate levels at baseline that slightly increased.

Also shown in Figure 7.5 are 95% confidence intervals around each trajectory. The fact that the confidence intervals do not overlap indicates the adequacy of the model.

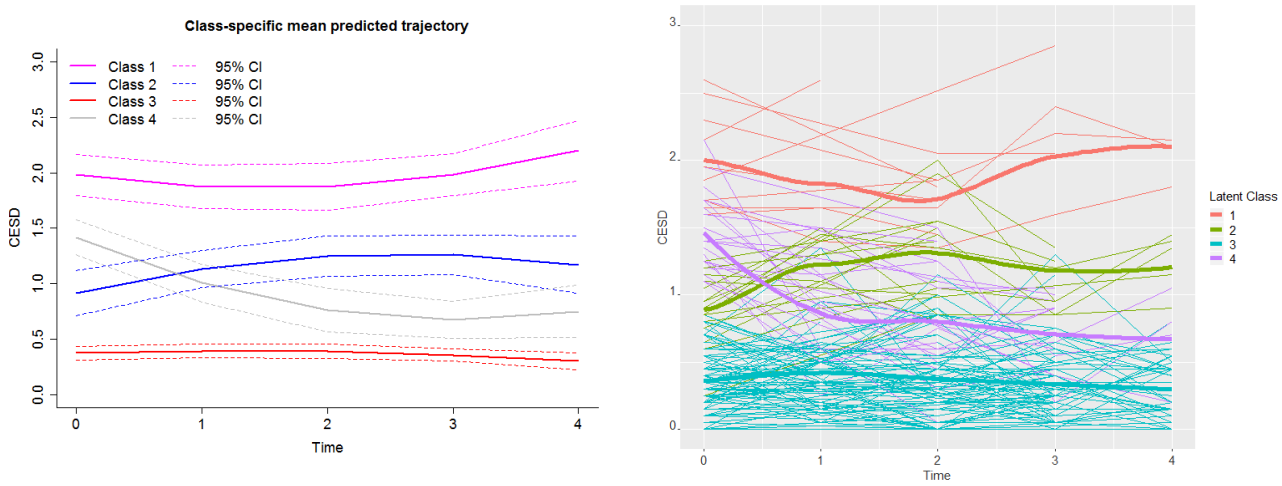

Figure 26. Mean predicted depression trajectories and spaghetti plot (each thin line connects the responses for the same patient over time) with the mean CES-D score at each measurement point for the four classes identified by the latent class model. Coding: Time 0:baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 24 months.

Factors associated with posttraumatic stress symptoms, functional impairment and depression trajectories

Associations between participant characteristics at baseline and membership in the trajectory groups of with posttraumatic stress symptoms, functional impairment and depression are summarized in Table and Table XV.

Overall, few associations between sociodemographsics/medical characteristics and trajectory membership are evident. For PDS, trajectories 1 (declining PDS) and 2 (low PDS) had a significantly higher proportion of women who were born in Israeli. A statistically significant association is also observed for the type of treatment. Trajectory 3 has higher proportion of women that undergone only chemo. However, this trajectory is composed of very few patients and pairwise tests between two trajectories at a time were statistically insignificant. For CES-D, working status, income from work (yes/no) and income from disability pension (yes/no) differed significantly among the trajectory classes. For example, rising trajectory 3 of low depression has a higher proportion of patients not receiving disability pension and patients having income from work. For functional impairment, participation in the intervention and level of religious faith,

differ significantly among the trajectory classes. Physical symptoms at baseline are significantly associated with the distinct trajectories of the considered psychological outcomes. The lowest p-values are observed for mood swings and interference with a sense of feminity at baseline. Posttraumatic growth at baseline is the only psychological variable that was not significantly associated with differences among trajectory groups (Table XV). Positive cognitive-emotional regulation had also a week association.

Table XIV Results of chi-squared tests (p - values) between the trajectories of functional impairment, depression (CES-D) and posttraumatic stress symptoms (PDS) and patient characteristics (sociodemographic, medical and symptoms variables-categorical variables) at baseline.

	Functional impairment	CES-D	PDS
Participation in the intervention	0.0067	0.5399	0.6304
Age	0.4231	0.2597	0.4473
Stage	0.5330	0.4209	0.7916
Protocol	0.3979	0.4988	0.8819
Treatment	0.2884	0.1407	0.0217
Herceptin	0.0814	0.8528	0.5793
Hormonal	0.4596	0.9092	0.3930
Urban residence	0.1142	0.1439	0.3704
Marital status	0.7309	0.1488	0.9024
Israeli	0.1860	0.1271	0.0031
Have children	0.6965	0.5916	0.7525
Work status	0.4779	0.0240	0.1554
Income from work	0.4574	0.0201	0.3869
Income from disability pension	0.3554	0.0045	0.7807
Income from pension	0.3307	0.6292	0.6110
Religious	0.0157	0.5195	0.2368
Carrier	0.5174	0.8185	0.8289
Family history	0.2879	0.5428	0.5659
Heat Waves	0.4297	0.1798	0.6156
Mood Swings	0.0019	0.0010	0.0012
Sleep Problems	0.1743	0.3723	0.0178
Obesity	0.0248	0.0217	0.1059
Decrease in comfort with the body	0.0077	0.2392	0.0579
Disruption in sexuality	0.0042	0.3212	0.0380
Inference with a sense of feminity	0.0003	0.0015	0.0016
Heat Waves: How much	0.1390	0.0009	0.0045
Mood Swings: How much	0.0000	0.0000	0.0000
Sleep Problems: How much	0.0037	0.0120	0.0000
Obesity: How much	0.0130	0.0327	0.0537
Decrease in comfort with the body: How much	0.0086	0.0872	0.0027
Disruption in sexuality: How much	0.0168	0.2049	0.0293
Inference with a sense of feminity: How much	0.0000	0.0000	0.0000

Table XV. Results of Anova tests (p - values) between the trajectory classes of functional impairment, depression (CES-D) and posttraumatic stress symptoms (PDS) and patient characteristics (sociodemographic and psychological variables-continuous variables) at baseline.

	Functional impairment	CES-D	PDS
Children	0.3285	0.4169	0.5022
Age	0.1836	0.5425	0.2257
Today distress level	0.0000	0.0000	0.0000
Level of Perceived Resilience Today	0.0000	0.0000	0.0000
Amount of hope for the future	0.0002	0.0000	0.0005
PACT Average Flexibility	0.0000	0.0000	0.0000
PTG Post traumatic growth	0.7918	0.2069	0.9147
EGO Resilience	0.0010	0.0013	0.0025
Functional impairment	0.0000	0.0000	0.0000
CESD Total depression	0.0000	0.0000	0.0000
CERQ Positive	0.0300	0.0355	0.1289
CERQ Negative	0.0014	0.0000	0.0002
PDS Post traumatic stress symptoms	0.0000	0.0000	0.0000
PACT Forward Focus	0.0000	0.0000	0.0000
PACT Trauma Focus	0.0471	0.0564	0.0245
PACT Total Coping	0.0001	0.0000	0.0000
PACT Polarity	0.7356	0.4580	0.4986
PACT Discrepancy	0.0027	0.0000	0.0009
PACT Total Flexibility	0.0005	0.0002	0.0000
PTG I Relating to Others	0.7543	0.1176	0.6780
PTG II – New Possibilities	0.4279	0.2616	0.9106
PTG III – Personal Strength	0.7286	0.1764	0.8838
PTG IV - Spiritual Change	0.8630	0.7314	0.4779
PTG V - Appreciation of Life	0.8099	0.7168	0.7989
PTG SF I Relating to Others	0.1752	0.1112	0.6254
PTG SF II New Possibilities	0.2753	0.1743	0.4402
PTG SF III Personal Strength	0.9054	0.2827	0.7421
PTG SF IV Spiritual Change	0.8630	0.7314	0.4779
PTG SF V Appreciation of Life	0.2945	0.6847	0.2465
PTG SF (Short Form)	0.8425	0.2596	0.9017
CESD I - Depressed affect	0.0000	0.0000	0.0000
CESD II– Positive affect	0.0000	0.0000	0.0000
CESD III – Somatic symptoms	0.0000	0.0000	0.0000
CESD IV – Interpersonal	0.0000	0.0000	0.0000
PDS Re-experiencing	0.0000	0.0000	0.0000
PDS Avoidance	0.0000	0.0000	0.0000
PDS Arousal	0.0000	0.0000	0.0000

Test of independence between posttraumatic stress symptoms, functional impairment and depression trajectories

Pearson's chi-squared test showed the classification of posttraumatic stress symptoms, functional impairment and depression trajectories as significantly associated with each other (p-values<0.0001). Indicative associations are reported below:

- The vast majority of patients in the 'low' PDS group were also assigned to the 'low' depression group.
- The vast majority of patients in the 'low' PDS group or the 'low' depression group were assigned to the 'low' functional impairment group.
- The vast majority of patients in the 'declining' PDS group belong either to the 'low' or 'declining' depression group.
- The majority of patients in the 'declining' PDS group belong to the 'declining' functional impairment group.
- Almost all patients in the 'high' depression group were assigned to the 'high' functional impairment group.

6.5.2 HUS dataset

Analysis plan

A latent-class mixed-effects regression analysis was performed in order to identify sub-groups of patients with distinct trajectory patterns of the psychological variables. The analysis was performed using the lcmm package of R. A linear and a quadratic model of the change across time was considered. Models with one to five latent growth classes ware fit to the data. Each model was run several times from different sets of initial values (typically from a grid of initial values) to avoid convergence to local minima. The number of latent growth classes that best fit the data were assessed by identifying the model with the lowest AIC. Furthermore, the minimal class size should be at least 8 patients and the average posterior probability of class membership should be above 0.7. After identifying the latent class solution that best fit the data, differences among the predicted classes were examined for important covariates and concurrent outcomes outside the models. Analyses of variance (ANOVA) and chi-squared analyses were used to assess for differences in demographic and clinical characteristics, symptom severity scores and other psychological outcomes of interest at baseline among the GMM latent classes. Alternative approaches (consideration of covariates in class membership and/or mixture model, multivariate modelling, consideration of alternative link functions) is work in progress. Indicative results are presented below for C30 global quality of life, C30 emotional functioning and B23 body image.

C30 Global quality of life

For C30 Global quality of life (QoL) variable, the best fitting unconditional model was the quadratic one with four classes. Figure 27 shows the resulting trajectories for the four-group model and the actual measurements of the patients that compose each class. The majority of patients (65.12%) were assigned to a class (labeled class 2) with relatively stable levels of high QoL across assessment points. Two classes evidenced decreasing QoL, but with different quadratic patterns. For the first class (7.17 % - labeled class 1), QoL gradually declined the second and third year after baseline. For the other one (15.5% - labeled class 3) the decline of QoL was

manifested the first year. The final class (12.21% - labeled class 4) is characterized by low initial but increasing QoL across assessment points.

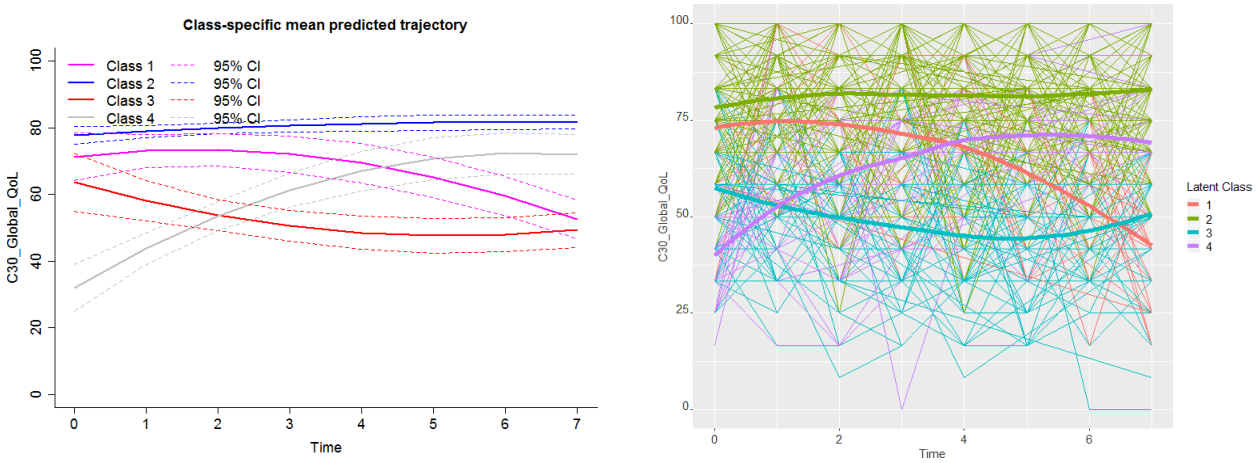

Figure 27. Mean predicted C30 global quality of life trajectories and spaghetti plot (each thin line connects the responses for the same patient over time) with the mean C30 QoL score at each measurement point for the four classes identified by the latent class model. Coding: Time 0: baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 18 months; Time 5: 24 months; Time 6: 30 months; Time 7: 36 months.

C30 Emotional functioning

For C30 Emotional functioning, the model that best described the data was the quadratic one with five latent classes. Figure 28 shows the resulting trajectories for the five-group model and the actual measurements of the patients that compose each class. The largest trajectory group accounted for 68% of the patients (labeled class 2) and was composed of patients who generally had relatively high levels of emotional functioning throughout the three-year period. The trajectory labeled class 5, estimated to account for 20.7% of the patients, had moderate average levels of emotional functioning over the three years. Two classes evidenced decreasing QoL, but with different quadratic patterns. For the first class (4.3 % - labeled class 4), QoL gradually declined the second and third year after baseline. For the other one (3.5% - labeled class 1) the decline of QoL was manifested the first year. The final group, labeled class 3 and accounting for 3.5% of the population, had relatively low levels of emotional functioning at baseline that considerably increased.

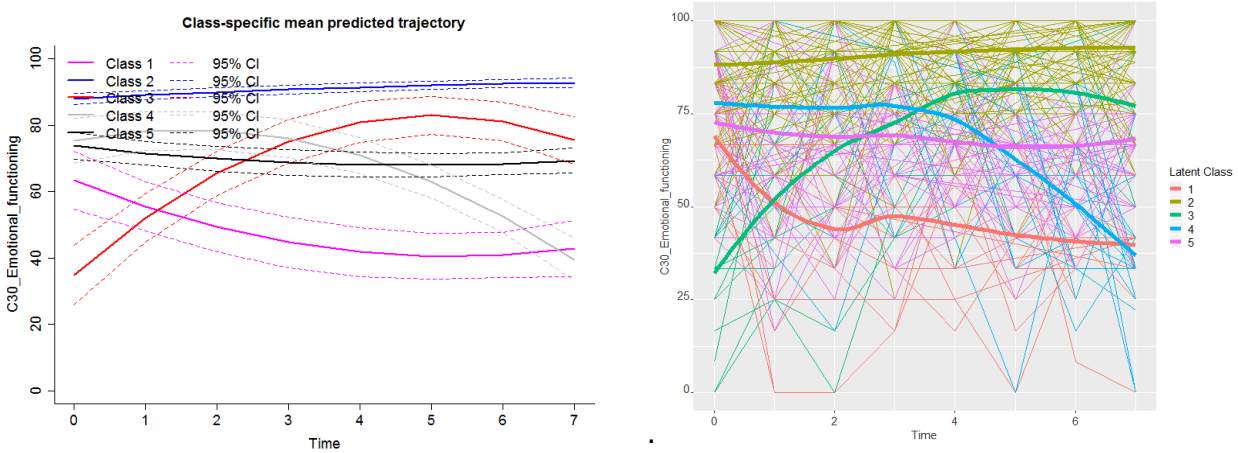

Figure 28. Mean predicted C30 emotional functioning trajectories and spaghetti plot (each thin line connects the responses for the same patient over time) with the mean C30 score at each measurement point for the four classes identified by the latent class model. Coding: Time 0: baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 18 months; Time 5: 24 months; Time 6: 30 months; Time 7: 36 months.

B23 Body Image

For B23 Body Image scale, the model that best described the data was the quadratic one with five latent classes. Figure 29 shows the resulting trajectories for the five-group model and the actual measurements of the patients that compose each class.

The largest trajectory group accounted for 58.1% of the patients (labeled class 4) and was composed of patients who generally had relatively high levels of body image throughout the three-year period or had initially low/moderate levels of body image that rise to high. The trajectory labeled class 5, estimated to account for 24.2% of the patients, is similar to class 4 but corresponds to moderate levels of body image. Class 3 (4.1%) is composed of patients with low initial levels that gradually increase to high across measurement points. Two classes (class 1 and 2) evidenced slightly decreasing levels of body image, but with different initial values.

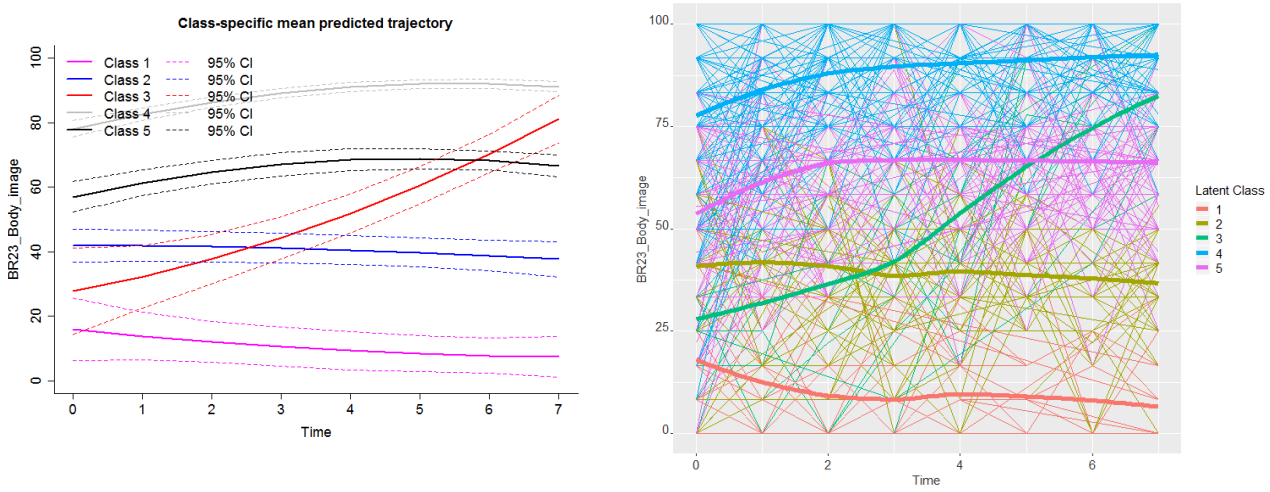

Figure 29. Mean predicted B23 body image trajectories and spaghetti plot (each thin line connects the responses for the same patient over time) with the mean B23 score at each measurement point for the four classes identified by the latent class model. Coding: Time 0: baseline; Time 1: 3 months; Time 2: 6 months; Time 3: 12 months; Time 4: 18 months; Time 5: 24 months; Time 6: 30 months; Time 7: 36 months.

Factors associated with global quality of life, emotional functioning and body Image

Associations between participant characteristics at baseline and membership in the trajectory groups of global quality of life, emotional functioning and body Image are summarized in Table XVI and Table XVII.

Table XVI. Results of chi-squared tests (p - values) between the trajectories of functional impairment, depression (CES-D) and posttraumatic stress symptoms (PDS) and patient characteristics (sociodemographic, medical and symptoms variables-categorical variables) at baseline.

	C30 Emotional Functioning	C30 Global QoL	B23 Body Image
Menopause status before therapy	0.1262	0.2423	0.1147
Hormone replacement therapy	0.8498	0.0407	0.0051
Breast surgery	0.2864	0.6965	0.6571
Axillary surgery	0.9918	0.0494	0.0000
Histological type	0.7328	0.9467	0.7475
Histological grade	0.5364	0.0511	0.1789
CT regimen	0.8710	0.4577	0.0089
Neoadjuvant therapy	0.8268	0.4449	0.3204
Herceptin	0.5950	0.3692	0.1031
ET	0.4765	0.7321	0.4897
ET agent	0.0092	0.4782	0.2366
Radiotherapy	0.6716	0.1759	0.3865
RT breast	0.7182	0.6628	0.3687
RT lymph nodes	0.8950	0.4906	0.0000
Marital status	0.0268	0.8486	0.7010
State of health	0.0024	0.0188	0.3430
Disability	0.0017	0.0000	0.0000
Psychatric disease	0.0004	0.7816	0.9224
Severe headache	0.2457	0.6331	0.1513
Urinary symptoms	0.7350	0.0037	0.4306

Table XVII. Results of Anova tests (p - values) between the trajectory classes of C30 emotional functioning, C30 quality of life (QoL) and B23 body image and patient characteristics (sociodemographic and psychological variables-continuous variables) at baseline.

	C30 Emotional Functioning	C30 Global QoL	B23 Body Image
Age	0.1182	0.9044	0.9203
Student years	0.3696	0.3532	0.7736
Degree of disability in work	0.0000	0.0000	0.0004
Degree of disability in leasure time	0.0000	0.0000	0.0002
Back pain	0.0053	0.0000	0.1585
Neck pain	0.0021	0.0000	0.1721
Proximal shoulder pain	0.0001	0.0000	0.1133
Distal shoulder pain	0.0029	0.0001	0.1340
Hip pain	0.7721	0.0028	0.1665
Knee pain	0.0102	0.2744	0.1348
Beer	0.5532	0.1605	0.0000
Long drink	0.8103	0.0543	0.1617
Strong alcvolohol	0.1884	0.1991	0.6567
Wine	0.0650	0.0949	0.8902
Cider or light wine	0.0000	0.7395	0.2517
Daily number of cigarrettes	0.0000	0.1763	0.0191
Duration of working day	0.1243	0.6503	0.8579
Exercise work duration	0.5277	0.5225	0.7117
Walking test result	0.0648	0.0002	0.0014
Waist circumference	0.7867	0.0023	0.0056
C30 Global QoL	0.0000	0.0000	0.0000
C30 Physical functioning	0.0000	0.0000	0.0000
C30 Role functioning	0.0000	0.0000	0.0000
C30 Emotional functioning	0.0000	0.0000	0.0000
C30 Cognitive functioning	0.0000	0.0000	0.0000
C30 Social functioning	0.0000	0.0000	0.0001
C30 Fatigue	0.0000	0.0000	0.0000
C30 Nausea nd vomiting	0.0104	0.0000	0.2092
C30 Pain	0.0000	0.0000	0.0000
C30 Dyspnea	0.0520	0.0001	0.0000
C30 Insomnia	0.0000	0.0000	0.0000
C30 ppetite loss	0.0057	0.0000	0.0187
C30 Constipation	0.7644	0.1475	0.8454
C30 Diarrhea	0.0404	0.0001	0.0069
C30 Fincial impact	0.0000	0.0000	0.0000
BR23 Body image	0.0000	0.0000	0.0000
BR23 Sexual functioning	0.3514	0.0002	0.0004
BR23 Sexual enjoyment	0.0915	0.0713	0.3644
BR23 Future perspective	0.0000	0.0000	0.0000
BR23 Systemic therapy side effects	0.0000	0.0000	0.0000
BR23 Breast symptoms	0.0000	0.0000	0.0043
BR23 Arm symptoms	0.0000	0.0000	0.0010
BR23 Upset by hair loss	0.0020	0.1139	0.0000

Test of independence between global quality of life, emotional functioning and body Image

Pearson's chi-squared test showed the classification of global quality of life, emotional functioning and body Image trajectories as significantly associated with each other (p-values<0.0001). Indicative associations are reported below:

- The vast majority of patients in the 'high' QoL group were also assigned to the 'high' emotional functioning group or the 'high' body image group.
- The vast majority of patients in the 'fast declining' emotional group 3 were assigned to the 'fast declining' QoL group 3.
- The vast majority of patients in the 'rising' emotional group belong either to the 'low' or to the 'declining' depression group.
- The patients in the (more gradually) declining emotional group 4 are equally distributed to the 'high' and 'declining' QoL groups.
- The majority of patients in the (more gradually) declining QoL group 1 belong to the highest trajectories 4 and 5 of body image.
- The vast majority of patients in the 'rising' body image group belong either to the 'high' or to the 'rising' QoL group.

6.6 A preliminary model - Testing the predictive ability of the framework

The aim to test whether the developmental trajectory of the psychological outcome of interest can be predicted for a new patient, based on the sociodemographic and medical characteristics, as well as her psychological profile at baseline.

We will consider the PDS trajectories of posttraumatic stress symptoms as identified in section 6.5.1. A Naïve Bayes and a Random Forest classifier will be trained and validated based on HUJI data and the assignment of the patients to the four PDS trajectory classes (low class 2, high class 4, declining class 1, rising class 3) derived by applying mixture modelling (section 6.5.1). The aim is to assess the predictive ability of the classifier, i.e. the ability to correctly assign the patients to the various developmental patterns of posttraumatic stress symptoms based on patient characteristics at baseline. The workflow for the development and validation of the classifiers consists of the following steps:

- *Identification* of distinct PDS trajectories that best describe the data and *assignment* of patients to each trajectory by applying mixture modelling (section 6.5.1).
- *Feature selection*: Based on chi-squared and ANOVA tests (Table XIV & Table XV) the covariates with p-value <0.05 in HUJI dataset at baseline have been selected, i.e. the clinical sociodemographic and psychological variables at baseline that differ (based on the above tests) across PDS trajectories.
- *Training* a Naïve Bayes and a Random Forest classifier with the selected features.
- *Cross-Validation*: The classifier was validated by applying 10-fold cross-validation repeated 5 times.

The accuracy of the Naïve Bayes and the Random Forest classifier are 0.81 and 0.83 respectively (Table XVIII & Table XIX). Both classifiers are not able to predict which patients with low/moderate initial levels of PDS had a temporary rise in PDS score over the 2 years (rising class 3). However, they predict most of the patients with moderate or higher initial levels of 'PDS' value that decreased to low levels by the end of the two-year observation period (declining class 1). The precision and sensitivity is high for the low-class 2 and high-class 4 PDS trajectories. Overall, the results can be characterized as promising, since the analysis of the data is still on going, the machine learning approaches used here are indicative and the retrospective data are limited in respect to the BOUNCE concepts.

Table XVIII. Confusion matrix of Naïve Bayes performance

		Actual class				
		Declining Class 1	High Class 4	Low Class 2	Rising Class 3	**Precision**
Predicted class	Declining	46	23	24	0	0.494624
	High	10	57	4	0	0.802817
	Low	13	0	364	30	0.894349
	Rising	1	0	3	0	0
	Sensitivity	0.657143	0.7125	0.921519	0	

Table XIX. Confusion matrix of Random Forest performance

		Actual class				
		Declining Class 1	High Class 4	Low Class 2	Rising Class 3	**Precision**
Predicted class	Declining	50	12	15	0	0.649351
	High	11	61	5	0	0.792208
	Low	9	7	364	30	0.887805
	Rising	0	0	11	0	0
	Sensitivity	0.714286	0.7625	0.921519	0	

7. Conclusions

The current deliverable presents the initial design and implementation of the preliminary resilience trajectory predictor within BOUNCE. All the computational approaches for the prospective BOUNCE data analysis are outlined according to four clinical scenarios that have been defined. The proposed computational scheme that will be developed can be used at any point during the course of diagnosis and treatment; thus, enabling the identification of patients at risk for poor psychosocial and functional outcomes. Cross-sectional and longitudinal data will be exploited by unsupervised and supervised machine learning techniques aiming at identifying patterns of patients' symptoms and at predicting final and intermediate outcomes at each and across different time points, respectively. A model fusion computational framework is also described which will enhance the predictive outcomes of the developed models. Furthermore, the models repository and the in silico prediction repository are also described in the present deliverable providing all the necessary information for the storage of models and their outcomes within the final BOUNCE platform, respectively. The security issues related to the integration of these different components within the platform are also described.

Finally, the deliverable includes indicative results of the trajectory analyses performed based on retrospective datasets. The analyses have been conducted in the framework of growth mixture modelling and include: a) Subjective criteria-based trajectory analysis, b) Mixed-effects linear regression analysis: Covariate effect on average trajectory, c) Latent-class mixed-effects analysis: identification of clusters of developmental trajectories, d) multivariate trajectory modelling, e) investigation of the predictive power of covariates on class membership, f) development of preliminary models that predict class membership based on patient characteristics at baseline.

References

Andreev VP, Liu G, Yang CC, Smith AR, Helmuth ME, Wiseman JB, Merion RM, Weinfurt KP, Cameron AP, Lai HH, Cella D, Gillespie BW, Helfand BT, Griffith JW, DeLancey JOL, Fraser MO, Clemens JQ, Kirkali Z, Group LS. Symptom Based Clustering of Women in the LURN Observational Cohort Study. J Urol 2018;200(6):1323-1331.

Bi XA, Xu Q, Luo X, Sun Q, Wang Z. Weighted Random Support Vector Machine Clusters Analysis of Resting-State fMRI in Mild Cognitive Impairment. Front Psychiatry. 2018;9:340. Published 2018 Jul 25

A. Brédart, O. Merdy, B. Sigal-Zafrani, C. Fiszer, S. Dolbeault, and J. Hardouin, "Identifying trajectory clusters in breast cancer survivors' supportive care needs, psychosocial difficulties, and resources from the completion of primary treatment to 8 months later," Supportive Care in Cancer, vol. 24, pp. 357-366, 2016

Bower JE, Wiley J, Petersen L, Irwin MR, Cole SW, Ganz PA. Fatigue after breast cancer treatment: Biobehavioral predictors of fatigue trajectories. Health Psychol 2018;37(11):1025-1034.

Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs 2010;14(2):101-110. doi: 10.1016/j.ejon.2009.09.005

Hiyoshi A, Fall K, Bergh C, Montgomery S. Comorbidity trajectories in working age cancer survivors: A national study of Swedish men. Cancer Epidemiol 2017;48:48-55

Genolini C, Ecochard R, Benghezal M, Driss T, Andrieu S, Subtil F. kmlShape: An Efficient Method to Cluster Longitudinal Data (Time-Series) According to Their Shapes. PLoS One 2016;11(6):e0150738.

Kant J, Czisch A, Schott S, Siewerdt-Werner D, Birkenfeld F, Keller M. Identifying and predicting distinct distress trajectories following a breast cancer diagnosis - from treatment into early survival. J Psychosom Res 2018;115:6-13

Kondo Y, Salibian-Barrera M, Zamar R. RSKC: An R Package for a Robust and Sparse K-Means Clustering Algorithm. Journal of Statistical Software 2016, 72(5), 1 - 26.

Kuncheva, L. I., Whitaker, C. J., Shipp, C. A., & Duin, R. P. (2003). Limits on the majority vote accuracy in classifier fusion. Pattern Analysis & Applications, 6(1), 22-31.

Leventhal, H., Halm, E., Horowitz, C., Leventhal, E. A., Ozakinci, G., Sutton, S., ... & Johnston, M. (2004). The SAGE handbook of health psychology.

Leventhal, H., Weinman, J., Leventhal, E. A., & Phillips, L. A. (2008). Health psychology: The search for pathways between behavior and health. Annu. Rev. Psychol., 59, 477-505.

Leventhal, H., Phillips, L. A., & Burns, E. (2016). The Common-Sense Model of Self-Regulation (CSM): A dynamic framework for understanding illness self-management. Journal of behavioral medicine, 39(6), 935-946.

Oermann EK, Rubinsteyn A, Ding D, Mascitelli J, Starke RM, Bederson JB, Kano H, Lunsford LD, Sheehan JP, Hammerbacher J, Kondziolka D. Using a Machine Learning Approach to Predict Outcomes after Radiosurgery for Cerebral Arteriovenous Malformations. Sci Rep 2016;6:21161

A. Pande, L. Li, J. Rajeswaran, J. Ehrlinger, U. B. Kogalur, E. H. Blackstone, et al., "Boosted multivariate trees for longitudinal data," Machine learning, vol. 106, pp. 277-305, 2017

Ruta, D., & Gabrys, B. (2005). Classifier selection for majority voting. Information fusion, 6(1), 63-81.

Raschka, S. (2018). MLxtend: Providing machine learning and data science utilities and extensions to Python's scientific computing stack. The Journal of Open Source Software, 3(24).

Winters ZE, Afzal M, Balta V, Freeman J, Llewellyn-Bennett R, Rayter Z, Cook J, Greenwood R, King MT, Group PTM. Patient-reported outcomes and their predictors at 2- and 3-year follow-up after immediate latissimus dorsi breast reconstruction and adjuvant treatment. Br J Surg 2016;103(5):524-536.

Y. Yang, J. Cameron, C. Bedi, and G. Humphris, "Fear of cancer recurrence trajectory during radiation treatment and follow-up into survivorship of patients with breast cancer," BMC cancer, vol. 18, p. 1002, 2018

Ferraiolo, D. F., & Kuhn, D. R. (1992). Natl Institute of Standards and Tech., Dept. of Commerce, Maryland, Role-Based Access Control. In Proceedings of 15th Natl Computer Security Conference.

H Andruff, N Carraro, A Thompson, P Gaudreau, B Louvet, Latent Class Growth Modelling: A Tutorial, Tutorials in Quantitative Methods for Psychology 2009, Vol. 5(1), p. 11-24.

Proust-Lima C, Philipps V, Liquet B (2017). Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm. Journal of Statistical Software, 78(2), 1-56. doi:10.18637/jss.v078.i02

Bryk AS, Raudenbush SW. 1987. Application of hierarchical linear models to assessing change. Psychol. Bull. 101:147–58

Goldstein H. 1995. Multilevel Statistical Models. London: Arnold

McArdle JJ, Epstein D. 1987. Latent growth-curves within developmental structural equation models. Child Dev. 58:110–33

Meredith W, Tisak J. 1990. Latent curve analysis. Psychometrika 55:107–22

Muthén B. 1989. Latent variable modeling in heterogeneous populations. Psychometrika 54:557–85

Willett JB, Sayer AG. 1994. Using covariance structure-analysis to detect correlates and predictors of individual change over time. Psychol. Bull. 116:363–81

Hipp JR, Bauer DJ (2006). Local Solutions in the Estimation of Growth Mixture Models. Psychological methods, 11(1), 36 :53

Bauer, D. J., & Curran, P. J. (2004). The integration of continuous and discrete latent variable models: Potential problems and promising opportunities. Psychological Methods, 9, 3–29.

Nagin, D. S. (1999). Analyzing developmental trajectories: A semiparametric, group-based approach. Psychological Methods,4,139–157.

Nagin DS, Land KC. 1993. Age, criminal careers, and population heterogeneity: specification and estimation of a nonparametric, mixed Poisson model. Criminology 31:327–62

Muthén, B. O., & Shedden, K. (1999). Finite mixture modeling with mixture outcomes using the EM algorithm. Biometrics, 55, 463–469.

Nagin DS, Odgers CL., Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol. 2010;6:109-38. doi: 10.1146/annurev.clinpsy.121208.131413.

Kreuter, F., & Muthén, B. (2007). Longitudinal modeling of population heterogeneity: Methodological challenges to the analysis of empirically derived criminal trajectory profiles. In G. R. Hancock & K. M. Samuelsen (Eds.), Advances in Latent Variable Mixture Models. Charlotte, NC: Information Age Publishing

T. Jung and KA Wickrama. An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. Social and Personality Psychology Compass, 2: 302-317. 2008. doi:10.1111/j.1751-9004.2007.00054.

N. Ram and K. J. Grimm Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups, Int J Behav Dev. 2009; 33(6): 565–576.

Redner R, Walker H (1984). “Mixture Densities, Maximum Likelihood and the EM Algorithm.” SIAM Review, 26(2), 195–239. doi:10.1137/1026034.

Muthén, B. O., & Muthén, L. K. (2001). Mplus: Statistical analysis with latent variables user’s guide (2nd ed.). Los Angeles: Stat Model.

Jones, B. L., Nagin, D. S., & Roeder, K. (2000). A SAS procedure based on mixture models for estimating developmental trajectories. Sociological Methods & Research, 29, 374–393.

P. E. Bidstrup, J. Christensen, B. G. Mertz, N. Rottmann, S. O. Dalton, and C. Johansen, "Trajectories of distress, anxiety, and depression among women with breast cancer: Looking beyond the mean," Acta Oncol. (Madr)., vol. 54, no. 5, pp. 789–796, 2015.

S. C. Danhauer, G. Russell, L. D. Case, S. J. Sohl, R. G. Tedeschi, E. L. Addington, K. Triplett, K. J. Van Zee, E. Z. Naftalis, B. Levine, and N. E. Avis, "Trajectories of Posttraumatic Growth and Associated Characteristics in Women with Breast Cancer," Ann. Behav. Med., vol. 49, no. 5, pp. 650–659, 2015.

K. A. Donovan, B. D. Gonzalez, B. J. Small, M. A. Andrykowski, and P. B. Jacobsen, "Depressive symptom trajectories during and after adjuvant treatment for breast cancer," Ann. Behav. Med., vol. 47, no. 3, pp. 292–302, 2014.

L. B. Dunn, B. A. Cooper, J. Neuhaus, C. West, S. Paul, B. Aouizerat, G. Abrams, J. Edrington, D. Hamolsky, and C. Miaskowski, "Identification of Distinct Depressive Symptom Trajectories in Women Following Surgery for Breast Cancer," Heal. Psychol., vol. 30, no. 6, pp. 683–692, 2011.

V. S. Helgeson, P. Snyder, and H. Seltman, "Psychological and Physical Adjustment to Breast Cancer over 4 Years: Identifying Distinct Trajectories of Change," Heal. Psychol., vol. 23, no. 1, pp. 3–15, 2004.

I. Henselmans, V. S. Helgeson, H. Seltman, J. de Vries, R. Sanderman, and A. V. Ranchor, "Identification and Prediction of Distress Trajectories in the First Year After a Breast Cancer Diagnosis," Heal. Psychol., vol. 29, no. 2, pp. 160–168, 2010.

Lam WW, Bonanno GA, Mancini AD, Ho S, Chan M, Hung WK, Or A, Fielding R., Trajectories of psychological distress among Chinese women diagnosed with breast cancer. Psychooncology. 2010 Oct;19(10):1044-51. doi: 10.1002/pon.1658.

W. W. T. Lam, I. Soong, T. K. Yau, K. Y. Wong, J. Tsang, W. Yeo, J. Suen, W. M. Ho, W. K. Sze, A. W. Y. Ng, A. Kwong, D. Suen, R. Fielding, "The evolution of psychological distress trajectories in women diagnosed with advanced breast cancer: A longitudinal study," Psychooncology., vol. 22, no. 12, pp. 2831–2839, 2013.

N. Rottmann, D. G. Hansen, M. Hagedoorn, P. V. Larsen, A. Nicolaisen, P. E. Bidstrup, H. Würtzen, H. Flyger, N. Kroman, and C. Johansen, "Depressive symptom trajectories in women affected by breast cancer and their male partners: a nationwide prospective cohort study," J. Cancer Surviv., vol. 10, no. 5, pp. 915–926, 2016.

Wang AW, Chang CS, Chen ST, Chen DR, Hsu WY., "Identification of posttraumatic growth trajectories in the first year after breast cancer surgery," Psychooncology., vol. 23, no. 12, pp. 1399–1405, 2014.

J. Brunet, S. Amireault, M. Chaiton, and C. M. Sabiston, "Identification and prediction of physical activity trajectories in women treated for breast cancer," Ann. Epidemiol., vol. 24, no. 11, pp. 837–842, 2014.

D. Nagin "Group-Based Modeling of Development ." Harvard University Press , Cambridge , 2005.

D. Nagin and C. L. Odgers, "Group-Based Trajectory Modeling in Clinical Research," Ssrn, 2010.

Robert D. Gibbons, Donald Hedeker, and Stephen DuToit, Advances in Analysis of Longitudinal Data, Annu Rev Clin Psychol. 2010 Apr 27; 6: 79–107.

D. Hedeker & R. D. Gibbons, Longitudinal Data Analysis, Published by John Wiley & Sons, Inc., Hoboken, New Jersey. 2006

Tony Jung and K. A. S. Wickrama, An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling, Social and Personality Psychology Compass 2/1 (2008): 302–317

Proust-Lima, Sene, Taylor and Jacqmin-Gadda (2014). Joint latent class models of longitudinal and time-to-event data: a review. Statistical Methods in Medical Research 23, 74-90.

Lucas CP, Zhang H, Fisher PW, Shaffer D, Regier DA, Narrow WE, et al. The DISC Predictive Scales (DPS): Efficiently screening for diagnoses. J Am Acad Child Adolesc Psych 2001;40:443 – 9.

Saarto T, Penttinen HM, Sievänen H, Kellokumpu-Lehtinen PL, Hakamies-Blomqvist L, Nikander R, Huovinen R, Luoto R, Kautiainen H, Järvenpää S, Idman I, Utriainen M, Vehmanen L, Jääskeläinen AS, Elme A, Ruohola J, Palva T, Vertio H, Rautalahti M, Fogelholm M, Blomqvist C and Luoma ML, Effectiveness of a 12-month exercise program on physical performance and quality of life of breast cancer survivors. Anticancer Res. 2012; 32(9):3875-84.

Hamama-Raz, Y., Perry, S., Pat-Horenczyk, R., Bar-Levav, R., Stemmer, S. (2012). Factors affecting participation in group intervention in patients after adjuvant treatment for early-study breast cancer. Acta Oncologica, 51, 208-214.

Pat-Horenczyk, R., Perry, S., Hamama-Raz, Y., Ziv, Y., Schramm-Yavin, S., Stemmer, S.M. (2015). Posttraumatic Growth in Breast Cancer Survivors: Constructive and Illusory Processes. Journal of Traumatic Stress, 28, 214-222. DOI: 10.1002/jts.22014. June 2015, 28, 214–222

Hamama-Raz, Y., Pat-Horenczyk, R., Perry, S., Ziv, Y., Bar-Levav, R., & Stemmer, S. M. (2016). The Effectiveness of Group Intervention on Enhancing Cognitive Emotion Regulation Strategies in Breast Cancer Patients: A 2-Year Follow-up. Integrative cancer therapies, 15(2), 175-182. DOI: 10.1177/1534735415607318.

Pat-Horenczyk, R., Saltzman, L. Y., Hamama-Raz, Y., Perry, S.., Ziv, Y., Ginat-Frolich, R., & Stemmer, S. M. (2016). Stability and Transitions in Posttraumatic Growth Trajectories among Cancer Survivors: LCA and LTA Analyses. Psychological Trauma: Theory, Research, practice and policy, 8(5), 541-5419. DOI: 10.1037/tra0000094.

Foa EB., Cashman L, Jaycox L, Perry K, The validation of a self-report measure of posttraumatic stress disorder: The Posttraumatic Diagnostic Scale. Psychological Assessment 1997:9(4), 445-451.

Radloff LS, The CES-D Scale: A Self-Report Depression Scale for Research in the General Population, Applied Psychological Measurement 1977:1(3):385 – 401.

Garnefski N, Kraaij V, Cognitive Emotion Regulation Questionnaire: Development of a short 18-item version (CERQ-short).Personality and Individual Differences 2006:41:1045-1053.

Bonanno, G. A., Pat-Horenczyk, R., & Noll, J. (2011). Coping flexibility and trauma: The Perceived Ability to Cope With Trauma (PACT) scale. Psychological Trauma: Theory, Research, Practice, and Policy, 3(2), 117-129.

Tedeschi, R. G., & Calhoun, L. G. (1996). The Posttraumatic Growth Inventory: Measuring the positive legacy of trauma. Journal of Traumatic Stress, 9(3), 455-472

Block, J., & Kremen, A. M. (1996). IQ and ego-resiliency: Conceptual and empirical connections and separateness. Journal of Personality and Social Psychology, 70, 349–361.

Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM.

Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002 Aug;32(6):959-76.

Weathers F, Litz B, Keane T, Palmieri T, Marx B.P, Schnurr P. The PTSD Checklist for DSM-5 (PCL-5) 2013

Cutillo A, O'Hea E, Person S, Lessard D, Harralson T, Boudreaux E., The Distress Thermometer: Cutoff Points and Clinical Use, Oncol Nurs Forum. 2017 May 1;44(3):329-336.

APPENDIX 1 ABBREVIATIONS

CHAMP	Fundação D. Anna de Sommer Champalimaud e Dr. Carlos Montez Champalimaud (Champalimaud Clinical Center - CCC)
FORTH	Foundation for Research and Technology – Hellas
HUJI	Hebrew University in Jerusalem, school of Social Work and Social Welfare
HUS	Helsinki University Hospital Comprehensive Cancer Center
ICCS	Institute of Communication and Computer Systems
IEO	European Institute of Oncology
NHG	NHG Consulting
NOONA	Noona Healthcare
SiLo	SINGULARLOGIC ANONYMI ETAIREIA PLIROFORIAKON SYSTIMATON KAI EFARMOGON PLIROFORIKIS