BOUNCE

Predicting Effective Adaptation to Breast Cancer to Help Women to

BOUNCE Back

BOUNCE NEWSLETTER

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BOUNCE MACHINE LEARNING MODELS PREDICT ONE-YEAR RESILIENCE OUTCOMES

By **Konstantina Kourou**, PhD, Unit of Medical Technology and Intelligence Information Systems, Institute of Molecular Biology & Biotechnology, Foundation for Research and Technology – Hellas, Ioannina, Greece, **Panagiotis Simos**, PhD, **Evangelos Karademas**, PhD, & **Giorgos Manikis**, PhD, Computational Bio-Medicine Laboratory, Institute of Computer Science, Foundation for Research and Technology-Hellas, Heraklion, Greece

In December of 2021 women who participated in the BOUNCE multinational prospective study completed the study scales and specially designed questionnaires at one year after breast cancer diagnosis. Immediately, the BOUNCE modeling team started work on the most challenging clinical question that can be reasonably addressed based on one-year follow up data: which factors render women more resilient to the challenges of breast cancer and cancer-related treatments?

To be included in the current analyses participants had to report no or very mild symptoms of anxiety or depression at the time of diagnosis of breast tumor associated with relatively high survival rates (Stage I-III). Resilience was defined by consistent absence of symptoms that generally indicate poor mental health (stable-good mental health group, comprising 393 women). The target (high risk) group comprised women who reported significant symptoms of anxiety and/or depression one year later (41 women). We focused on this group given that these women would merit rigorous prevention strategies.

Two complementary supervised machine learning models were computed. In the first we assessed overall accuracy to predict mental health deterioration by considering all potentially relevant variables, including mental health measures obtained within three months from cancer diagnosis. Additional potential predictors included:

- ***Life-style:*** Smoking, alcohol consumption, diet type, physical exercise
- ***Medical:*** ECOG performance status, obesity, family history of BC, pre-existing chronic physical illness, psychotropic medications, pre-existing anxiety or dysthymia, anemia, menopausal status, serum levels of alanine aminotransferase, creatinine, and bilirubin, blood cell count.
- ***Breast cancer-related:*** Cancer stage (I vs II or III), tumor molecular profile, estrogen receptor positivity, HER2 positivity, Ki67 levels, type and timing of cancer treatments (surgery, type of chemotherapy, radiotherapy, type of endocrine therapy, antiHeR2 treatment, systematic mental health support
- ***Psychosocial*** **characteristics** in the following domains: (i) personality characteristics, (ii) sense of coherence and control, (iii) the ability to cope with trauma, (iv) perceived social support, (v) resilience as trait, (vi) illness perception and related behaviors, (vii) overall QoL and (viii) patient affect at the time of measurement.

Feature selection, using a Random Forest algorithm, was incorporated into the Machine Learning pipeline to select only the relevant features for training and testing the final model. A 3-fold data split for hyper-parameters (i.e. cross-validation with grid search) was applied on the training, testing and validation subsets, to prevent overfitting and maximize model generalizability performance on the test set.

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This model correctly predicted one-year mental health deterioration for 70% of patients. Moreover, the model identified the patients who had stable good mental health status at one-year with approximately 75% certainty.

Personalized risk profiles

The second model entailed an identical pipeline and set of predictor variables as those used for Model 1 with one exception: self-reported ratings of anxiety, depression, and overall quality of life at the time of diagnosis or soon after (i.e., up to 3 months later) were not considered as predictors. In this manner we focused on potential modifiable factors such as life style and psychosocial characteristics of the patients. The model pipeline was supplemented by model-agnostic analyses to further explore the role of specific variables to a particular mental health prediction.

The break-down plots presented in Figure 1 illustrate the contribution of a subset of variables towards a correct prediction of Deteriorated Mental Health for a randomly selected participant. The 10 most highly ranked features selected by the model for this specific instance-level prediction are displayed here. The actual ratings provided by this patient on various study questionnaires within the first three months from diagnosis are shown next to the variable names. Nine variables appear to predispose toward an adverse mental health outcome for this patient: relatively high negative affect (e.g., fear, worry; throughout the first three months post-diagnosis), lower levels of resilience as a personal characteristic, the tendency to perceive illness as an uncontrollable source of anxiety and try to avoid any thoughts about it (at three months into the course of illness), combined with lack of physical exercise at the time of diagnosis, and relatively low levels of the perceived ability to manage adversities in general as well as cope with cancer particularly (as an initial response to the diagnosis). Conversely, relatively high scores on perceived social support (at month 3) appear to exert a protective role for this patient by reducing the probability for an adverse mental health outcome.

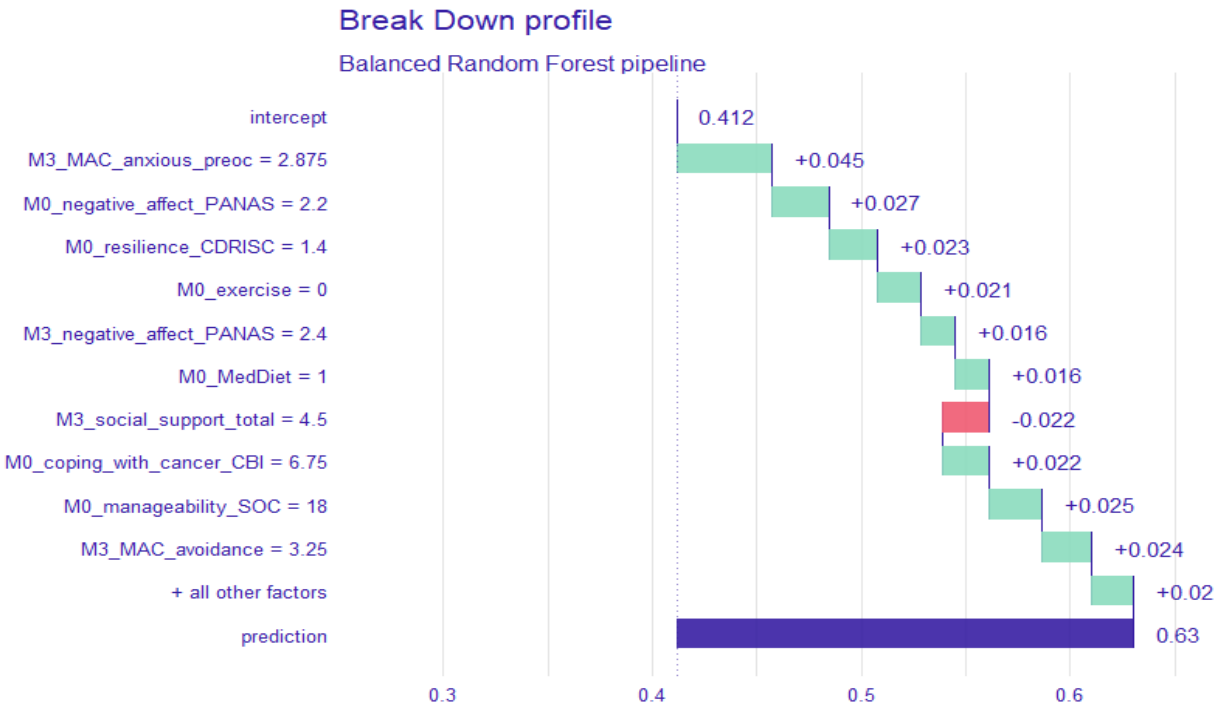

Figure 1. Break-down profile of a patient who displayed deteriorated mental health status at M12. Prediction probability is shown on the horizontal axis (Stable-Good mental health = 0, Deteriorated Mental Health =1). This patient was given a high probability of membership in the Deteriorated Mental Health class (0.63). A positive value assigned to a given score (green bars) indicates the degree of its contribution toward a prediction of Deteriorated Mental Health. A negative value (red bar) indicates the degree of a given score's contribution away from a prediction of Deteriorated Mental Health (i.e., increasing the probability of assigning this patient to the Stable-Good Mental Health class).

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The present results represent an important advance toward establishing the transparency and trustworthiness of machine learning applications to address mental health patient outcomes in clinical studies. On this basis, we employed patient-level interpretation techniques to identify key variables that contribute to the successful predictions for individual patients. In principle, indices of relative variable impact could help clinicians identify patient characteristics which may predispose toward, or have a protective role against, adverse mental health outcomes. Such predictions could be used in the future to guide personalized planning of psychological interventions. According to these models, adaptation to a severe health crisis is a complex process which is determined by: (a) a variety of personal (and interpersonal) resources (like expectations, lifestyle, or social support), which may buffer the negative impact of the situation and facilitate adaptation; (b) cognitive-emotional processes (e.g., affect and emotion regulation, self-efficacy to cope with cancer) that guide behavior (such as preoccupation,); (c) contextual and specific stressor-related factors that may impact adaptation (directly or indirectly; e.g., symptoms).

Future steps toward computational modeling of patient resilience

As 18-month follow up data become available to BOUNCE modelers, the prediction scope is increased and critical information on patient well-being can be reasonably assessed. Current modeling work focusses on multimodal variables which increase the risk of adverse mental health and quality of life outcomes beyond the first year from cancer diagnosis. More importantly, we continue to work on models identifying protective factors toward persistent psychosocial resilience.

FACING THE CONTINUOUS FEAR OF CANCER RECURRENCE

By **Gabi Bentley,** PhD candidate, **Osnat Zamir,** PhD, **Shlomit Perry**, PhD, **Rawan Dahabre,** PhD candidate & **Ruth Pat-Horenczyk**, PhD School of Social work and Social Welfare, The Hebrew University of Jerusalem

Women dealing with breast cancer face immediate and long-term emotional challenges, one of which is the fear of cancer recurrence. Fear of cancer recurrence refers to 'fear, worry, or concern relating to the possibility that cancer will come back or progress' (Lebel et al., 2016, p. 3265). Fear of cancer recurrence is a multidimensional construct, consisting beliefs about the chronicity and severity of cancer, and intense emotions about recurrence. Many cancer patients report that fear of cancer recurrence is constantly present or at the back of their mind.

How does the Fear of Cancer Recurrence impact breast cancer patients?

Fear of cancer recurrence is one of the most widespread experiences of survivors. It has been pointed out that fear of cancer recurrence may have a positive behavioral effect on survivors, such as adopting normative check-ups and general awareness of physical state. While at the same time, fear of cancer recurrence may impact day-to-day life, for example finding it hard to take part in meaningful and enjoyable activities. Furthermore, it may affect various life aspects such as quality of life, including, functioning at work, worrying about family members while feeling unpredictability and fear of death. Thus, fear of cancer recurrence can be manifested in a range of reactions, from a normative reaction to the possibility of cancer to recur or progress to an extreme level, which can become a clinically significant reaction of fear of cancer recurrence (Crist & Grunfeld, 2013; Lee-Jones et al., 1997).

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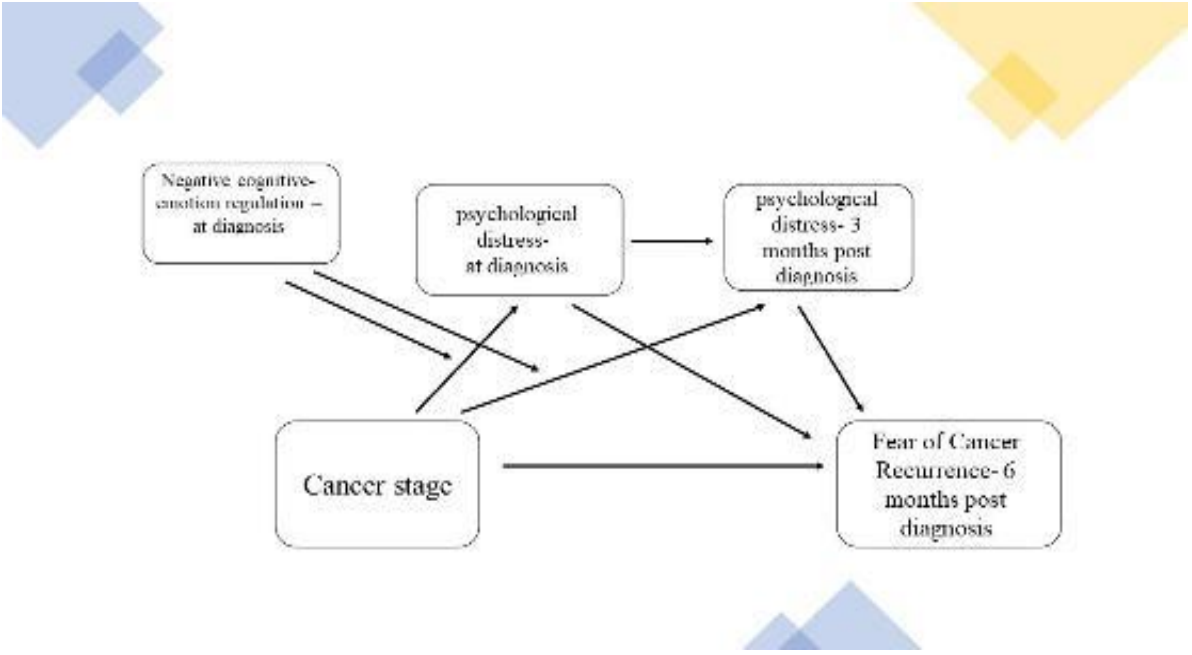
How the BOUNCE project can contribute to the understanding of Fear of Cancer Recurrence?

The Bounce study has provided the opportunity to investigate how fear of cancer recurrence develops over time and how it's associated with mental health and wellbeing among breast cancer patients. We examed several *risk* factors (such as the severity of the illness and type of treatment) and *protective factors* (e.g., coping strategies) as predicting the development of fear of cancer recurrence. Additionally, we explored the various trajectories of the fear of cancer recurrence and how these trajectories are linked to anxiety and depression. The BOUNCE project also provided the opportunity to perform cross-cultural analyzes and comparisons.

What did we find about the fear of cancer recurrence?

- We tested the fear of recurrence six months after the diagnosis of breast cancer. The level of fear could be predicted by the initial level of depression and anxiety of women around the time of the diagnosis with breast cancer.
- The cognitive emotional regulation coping strategies made a difference! Less negative emotional regulation strategies (a protective factor), mitigated the association between the severity of the illness and the fear of cancer recurrence as reported after six months. In other words, women who diminish or avoid using negative strategies will show more resilience, due to the reduced risk of developing mental distress. In fact, the tendency to self-blame, other-blame or use catastrophizing thoughts (e.g. "I keep thinking about how terrible it is what I have experienced"), may exacerbate emotional distress and this in turn may lead to higher levels of fear over the years.
- In a multicultural perspective, we found that the phenomenon of fear of cancer recurrence is universal and so are the factors influencing its development, relevant to all the women who participated in the study, regardless to the country of origin.



What are the clinical implications?

- It is important to recognize the concept of fear of cancer recurrence and its distinction from psychological distress i.e. anxiety and depression.
- To do this it is important to train professionals regarding the meaning of fear of cancer recurrence and its development over time.
- As noted, fear of cancer recurrence may manifest in effective and normative levels that will affect positively patient's health, compared to too high levels that may affect clinically the survivors quality of life and well-being
- Screening and treatment of depression and anxiety should be developed among breast cancer patients, already at time of receiving the diagnosis, in order to reduce the impact on the development of the fear of cancer recurrence.

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- Accordingly, it is important to develop treatment interventions in order to treat the fear of recurrence of the cancer.

What is needed next?

The BOUNCE project contributes to our clinical knowledge regarding fear of cancer recurrence and highlights a few main topics that should be prioritized. First, the need to expand the intervention programs geared for breast cancer patients to include the discussion of fear of cancer recurrence. Second, in the context of the current COVID-19 pandemic, there is a need to analyze the effects of on patients managing breast cancer, who are already at higher health risk and may face additional increased anxiety, uncertainty and fear of recurrence. Last, further studies are required to assess the fear of cancer recurrence among different types of cancer patients and age groups in order to promote higher quality of life and well-being for cancer survivors (Butow et al., 2021).

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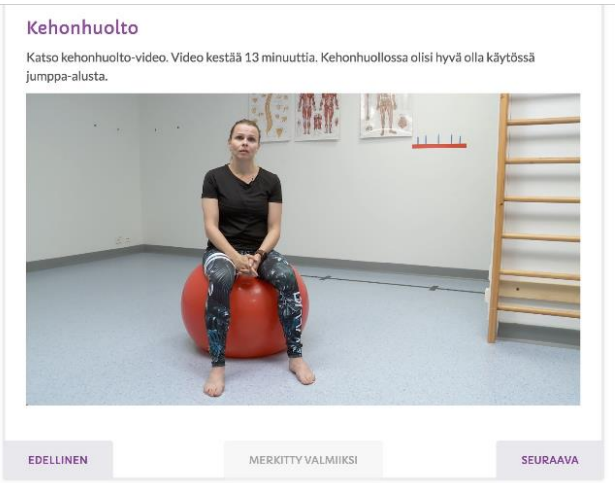
A PILOT STUDY OF A DIGITAL EXERCISE PATH AT THE HUS CENTER

By **Paula Poikonen-Saksela,** MD, BOUNCE Coordinator

Exercise has several positive effects among breast cancer survivors. Exercise is associated with lower mortality and lower risk for relapse (1), and improves physical health and quality of life (2). Accordingly, the amount and type of exercise carried out by the women who participate in the main BOUNCE study is recorded at 3-6 month intervals through cancer diagnosis and recovery

In anticipation of the results of the one-year mental health and quality of life prediction models we started preparing a digital intervention program targeting life-style changes. The online platform designed at HUS supports three different types of patient education interventions: (i) patient empowerment path, (ii) exercise path and (iii) nutrition path.

From December 2020 to November 2021 100 participants were recruited for an efficacy pilot study of the digital platform. The main goal of this study was to evaluate patient compliance with the intervention program. In addition, we assessed the functionality of the program workflow and its suitability for future use in clinical practice. We focused on patients who, at the time of cancer diagnosis, did not exercise according to the current recommendations for cancer patients (3).



An adequate amount of exercise was considered exercising at least 150 moderate aerobic exercise, or 75 minutes of hard exercise per week including at least 2

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times muscle work. Using this definition 80% of participants were guided to the exercise path. It is important to remember that even during the active treatment period of breast cancer patients can exercise and they should be as physically active as their abilities and conditions allow.

The exercise path was implemented through the HUS Health Village Platform which is a comprehensive digital service platform. This path comprises information links, exercise videos, exercise diary and monthly chat. It was designed to help participants be active from the start of their treatment period. The content of the platform was designed by two physiotherapists Katja Ristimäki and Minna-Leena Syrjälä with a long experience with breast cancer patients. The active intervention period is 10 weeks but the online material is available for up to one year. In the exercise path a walk in nature and chat was organized monthly or bimonthly depending on the COVID-19 situation. This walk offered participants a chance to meet peers as well as physiotherapists.

A pleasant walk also served as a venue for exchanging experiences on how to exercise during cancer treatments (frequency, type of exercise, recovery) and the effect of being in touch with nature on personal wellbeing. Preliminary compliance data from the first 22 patients, who completed the active intervention period, revealed an average of 15 logins on the platform per participant (range 2-27). This is already a promising finding which could reflect that there is a need of this type of intervention. When all participating patients complete at least 3 months of platform use we plan to assess compliance, quality of life, and amount of exercise in comparison with the sample from the main BOUNCE study.

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THE ROLE OF FOOD IN MAINTAINING HEALTH IN BREAST CANCER SURVIVORS

By **Chariklia Tziraki**, MD, PhD – HUJI team, Gabriela Ribeiro, RD, PhD, Champalimaud Clinical Center

As a breast cancer survivor, you can do something to moderate the likelihood of recurrence and maintain a good quality of life. One of the critical pathways to achieve a good quality of life and decrease the chances of recurrence, is to eat healthily. Additionally, healthy eating will help with other chronic diseases such as diabetes, hypertension, high cholesterol level, and heart disease, that breast cancer survivors may also have.

According to the most recent recommendations by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR): (1) maintaining healthy body weight, (2) being physically active, (3) following a high-fibre diet, and (4) limiting the intake of fats (in particular, saturated fatty acids) can improve overall survival after BC diagnosis . Thus, these "good practice guidelines" are likely to impact both overall survival and the risk of recurrence. Current evidence further suggests

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that consumption of vegetables, whole grains, fruits, fish and poultry and low consumption of red meat, refined foods, sweets, and high-fat dairy products might improve early-stage breast cancer overall prognosis and survival.

Being overweight or obese is associated with an increased risk of BC recurrence. Particularly, obesity is associated with poorer overall survival and increased mortality in post-menopausal BC women.

Thus, maintaining a healthy weight should be a primary goal for BC women. Weight management requires a multidisciplinary approach beyond healthy eating and physical activity. Many individual and environmental factors influence a patient's ability to maintain or lose weight, for which professional guidance is crucial. Importantly, effective implementation of the four pillars mentioned above, can be successfully implemented at home, as a recent study conducted during the Corona pandemic demonstrates.

It appears that losing weight, if obese, may be an essential factor in itself. Diets rich in plant sources are a vital part of getting to and staying at a healthy weight. For more specific instructions, including recipes and practical tips, please see:

https://www.cancer.org/treatment/survivorship-during-and-after-treatment/coping/nutrition/benefits.html

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RECENT EVENTS

4th DISSEMINATION EVENT: Let's talk about the resilience of women living with breast cancer

On the 8th of October 2021, the Champalimaud Foundation (CF) organized the fourth dissemination virtual event of the European Project BOUNCE: Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back as a scientific workshop. For more information about the event follow this link:

Read more…

THE BOUNCE PROJECT IN THE WINTER ISSUE OF EU RESEARCH MAGAZINE!

The Bounce Project is featured in the winter 2021 issue of EU Research magazine! In the article, Dr Paula Poikonen-Saksela explains how the BOUNCE Researchers are developing a model of patient resilience that can then be used to guide decision-making and help breast cancer patients to bounce back to healthy functioning.

Read more…

THE BOUNCE AUTOMATED DATA CLEANING PROCESS

The BOUNCE automated data cleaning process aims at detecting and correcting (or removing) any "messy", "noisy", corrupted or erroneous data entries of a dataset. To achieve this, it provides the configurable mechanism that increases the data quality of a dataset, which is usually composed of information originating from a variety of heterogeneous data sources, by increasing the cleanliness and completeness of the dataset to the highest possible degree.

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HOW AI MODELS CAN IMPROVE THE CLINICIANS' PERFORMANCE TO PREDICT PATIENTS' RESILIENCE DURING THE TREATMENT PROCESS

In order to gather clinical data, a part of the BOUNCE project is user experiments. This way data can be gathered and studied in order to improve understanding and the capacity to predict the resilience of women. The goal is to achieve more personalized interventions and eventually contribute to clinical outcomes and patient well-being

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