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Understanding and supporting oral medication adherence in breast cancer

M-PSI-1

MASSIMO PEZZOLATO
Matr. R13495
ORCID n. 0000-0003-2150-6695

Tutor
Prof. GABRIELLA PRAVETTONI

PhD coordinator
DIEGO PASINI

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List of abbreviations

AI: Artificial intelligence
APA: American Psychological Association
AUC: Area under the receiver operating characteristic curve
BC: Breast cancer
BCT: Behaviour change technique
BCTO: Behaviour Change Technique Ontology
BCTT: Behaviour Change Technique Taxonomy
BCW: Behaviour Change Wheel
BDI-II: Beck Depression Inventory II
BMQ: Beliefs about Medicines Questionnaire
CARE: Centre for Adherence Research and Education
COM-B: Capability, opportunity, motivation, and behaviour model
CSM: Common-sense model of self-regulation
DL: Deep learning
EORTC-QLQ-BR23: European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire
EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EV: External validity
HBM: Health belief model
HCP: Healthcare provider
IEO: European Institute of Oncology
IV: Internal validity
mBC: Metastatic breast cancer
MID: Minimal important difference
ML: Machine learning
MMWFY ©: Making Medicines Work For You
NCF: Necessity-concerns framework
NLP: Natural language processing
LLM: Large language model
P: Power
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROBAST: Prediction Model Risk of Bias Assessment Tool
RB: Reporting bias
SD: Standard deviation

SB: Selection bias

STAI-Y: State-Trait Anxiety Inventory

TTM: Transtheoretical model

TPB: Theory of planned behaviour

TRA: Theory of reasoned action

WHO: World Health Organization

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Abstract

Oral therapies are widely prescribed for the treatment of different types of cancer, including breast cancer, but, despite their convenience and apparent simplicity, relevant rates of non-adherence to oral medications have been reported. Non-adherence can lead to suboptimal clinical outcomes and increased economic burden on healthcare system.

The aim of this PhD thesis is to comprehensively address non-adherence in breast cancer, enhancing understanding of this phenomenon and supporting patients, particularly those with metastatic disease, in maintaining adherence to their oral therapies. In light of healthcare constraints and limited resources, special emphasis is placed on identifying individuals most likely to benefit from targeted interventions or additional support.

These objectives were addressed through a series of studies employing diverse design and methodologies. Three literature reviews were conducted: a systematic review of interventions aimed at improving adherence, a scoping review on predictive models of non-adherence, and a systematic review on the contribution of artificial intelligence to adherence. These reviews synthesised and organised existing knowledge, providing a foundation for the subsequent phases of this PhD project.

In addition, two original studies focused specifically on metastatic breast cancer patients. The first was a qualitative study comprising focus groups that explored patients' perceived barriers and facilitators to adherence, as well as their perspectives on digital tools for adherence support. The second was a pilot optimisation study assessing the feasibility and perceived usefulness of three intervention components (i.e., educational material, personalised reminders, and behavioural feedback) delivered according to a full factorial design, while also collecting data on adherence and relevant psychological variables.

Across all studies, adherence was confirmed as a multifactorial phenomenon, shaped by clinical, psychological, and relational factors. Interventions including prompts and behavioural feedback appeared most promising, while predictive models, even those using machine learning, showed limited accuracy and faced validation and implementation challenges. For metastatic patients, treatment side effects were a key barrier, whereas supportive patient-clinician relationships facilitated adherence. Digital tools were cautiously welcomed when enabling timely communication or peer support. Unexpectedly, metastatic breast cancer patients showed high adherence, partly explained by strong beliefs in the necessity of their treatment. Finally, a pilot multi-component intervention combining educational material, reminders, and behavioural feedback proved feasible, low-cost, and valued by patients.

In summary, this thesis advances the understanding of medication non-adherence in breast cancer, with a particular focus on patients with metastatic disease. The findings underscore the importance of tailored, patient-centred strategies that consider clinical, psychological, and relational factors, providing a foundation for future research and interventions aimed at supporting adherence and enhancing patient well-being.

"Keep a watch also on the faults of the patients,
which often make them lie about the taking of things prescribed.
For through not taking disagreeable drinks, purgative or other, they sometimes die."
Hippocrates, Decorum

1. Introduction

1.1 The phenomenon of non-adherence

Billions of dollars are spent every year in producing, researching, and developing new pharmaceuticals (Wouters & Kesselheim, 2024). Nonetheless, medicines can only be effective if patients actually take them. Contrary to common belief, a substantial proportion of patients across a wide range of conditions fail to take their medication as prescribed. This phenomenon is known as *medication non-adherence*.

The World Health Organization (WHO) defined adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (HCP) (World Health Organization, 2003, p. 3). This broad definition is intended to encompass not only actual medication-taking behaviours, but also the full range of therapeutic behaviours that may be subject to adherence, such as attending follow-up appointments, modifying one's diet, engaging in physical activity, and refilling medication prescriptions. Focusing on medication adherence, Cramer et al. offer a more specific definition: medication non-adherence refers to not taking medication at the time, in the dosage, or with the frequency prescribed by the HCP (Cramer et al., 2008).

In the past, the term *compliance* was more commonly used to describe a patient's adherence to a prescribed medication regimen. However, it has gradually been replaced by the term *adherence*. While compliance carries somewhat passive connotations, adherence implies a more active role for the patient, who participates in medical decision-making and actively commits to the agreed treatment plan. It is important to note from the outset that both compliance and adherence may be somewhat inadequate to fully describe this complex phenomenon, as they tend to place excessive emphasis on the role of HCPs while downplaying the patient's involvement. Nevertheless, adherence at least reflects a shift towards a more patient-centred approach, aligning better with contemporary healthcare perspectives.

Another concept closely related to adherence is *persistence,* It refers to the patient's behaviour of continuing to take a prescribed medication over the intended treatment period, capturing the extent to which therapy is maintained as planned (Brown & Bussell, 2011; Cramer et al., 2008; World Health Organization, 2003).
Non-adherence can be further differentiated into unintentional non-adherence, which occurs when the reasons are beyond a conscious personal decision (e.g., forgetting), and intentional non-adherence, when patients deliberately choose not to take their medication as prescribed (Lehane & McCarthy, 2007).

It has been estimated that approximately 50% of patients with chronic conditions do not adhere to their prescribed medication (Brown & Bussell, 2011; World Health Organization, 2003). Although this percentage can vary significantly depending on the condition, population characteristics, and the methods used to measure adherence, numerous studies in the scientific literature indicate concerning rates of non-adherence. For instance, medication non-adherence has been observed in more than 60% of patients with hypertension and hyperlipidaemia (Chantzaras & Yfantopoulos, 2025), while up to 50% of cardiovascular medications are discontinued within the first year of treatment (Nelson et al., 2024). Non-adherence rates among patients with type 2 diabetes have been reported to range from 44% to 67%, depending on the type of medication (Cai et al., 2017), and adherence to immunosuppressive medication in kidney transplant recipients can be as low as 22% (Melilli et al., 2025). Additionally, 74% of patients with major depressive disorder are non-adherent at 12 months (Keyloun et al., 2017), and non-adherence to antipsychotic medication exceeds 50% among patients with schizophrenia (Karabulut & Uslu, 2024).

The reasons for non-adherence are varied and can differ significantly depending on the specific condition, the type of treatment, the social context, individual characteristics, and the quality of the patient–HCP relationship. The WHO categorize the various adherence determinants in the following five categories: (1) socioeconomic-related factors, (2) healthcare team/health system-related factors, (3) condition-related factors, (4) therapy-related factors, and (5) patient-related factors (World Health Organization, 2003). An overview of 21 systematic reviews on factors influencing medication adherence evaluated the strength of evidence for each factor across a wide range of chronic conditions. Among the *socioeconomic factors* (e.g., social support, social context, stigma, environment, language, income, occupation, insurance), the authors identified that belonging to an ethnic minority is generally associated with lower adherence, whereas higher socioeconomic status tends to have a positive influence (Gast & Mathes, 2019; Peh et al., 2021). Some *healthcare team and health*

system-related factors include the patient–HCP relationship, communication quality, trust in the provider, continuity of care, and the cost of medication. (Peh et al., 2021). Among these factors, the requirement of co-payment has been associated with lower medication adherence, with sufficient supporting evidence (Gast & Mathes, 2019). *Patient-related factors* include cognitive and psychological aspects (e.g., beliefs, health literacy, concerns, emotions, motivation), demographics, quality of life, and family or caregiver characteristics (Peh et al., 2021). Although there are inconsistencies among the results of different studies and clinical populations, age appears to have a U-shaped relationship with adherence, with both younger and older patients showing lower adherence compared to those in the middle of the age distribution (Gast & Mathes, 2019; Pezzolato, Spada, et al., 2023). Among *condition-related factors* are the presence of symptoms, comorbidities, disease severity, and time since diagnosis (Peh et al., 2021). It has been consistently shown that general mental comorbidity, particularly depression, negatively impacts patient adherence (Gast & Mathes, 2019). Some *therapy-related factors* include the type of medication, complexity of the dosing regimen, side effects, and perceived benefits (Peh et al., 2021). However, the previously cited overview of systematic reviews on this topic failed to find sufficient evidence for a strong influence of any of these related factors on medication adherence (Gast & Mathes, 2019).
In summary, medication non-adherence emerges as a complex phenomenon with multifactorial determinants. Inconsistencies across different studies make it difficult to outline a clear model for the onset of non-adherence, and particularly challenging to predict or identify patients who may require support or targeted interventions.

Independently of its determinants, non-adherence to medication has a significant impact on clinical outcomes, leading to worse prognosis, avoidable hospitalizations, emergency care, outpatient visits, higher mortality rates, and increased economic costs. It is estimated that non-adherence costs approximately US$100 billion annually in the USA and €125 billion in Europe (Cutler et al., 2018; Kini & Ho, 2018; Organisation for Economic Co-operation and Development, 2018).

Given its significant consequences, it is not surprising that non-adherence has been extensively studied over the last decades. Nonetheless, the complexity of this phenomenon makes it particularly challenging to investigate (Brown & Bussell, 2011).
A first obstacle lies in the difficulty of accurately assessing and measuring medication adherence. Several measuring methods have been reported, and they can be broadly categorised into three groups: subjective measurements (e.g., self-reports, patient-reported outcomes, medication diaries, or information provided by family members,

caregivers, or healthcare professionals), objective measurements (e.g., pill counts, medication event monitoring systems, medical records, or pharmacy dispensing data), and biochemical measurements (e.g., adding markers to medication to track it through blood or urine analysis, or detecting drug metabolites in biological samples). None of these methods can be considered a gold standard; however, a combination of approaches is recommended, as each has its own strengths and limitations. For instance, biochemical measurements are considered the most reliable, but they are costly and challenging to repeat at multiple time points or to apply across large patient populations. On the other hand, self-reports are convenient and easy to administer, but they are susceptible to errors and distortions, and may lead to an overestimation of adherence (Cramer et al., 2008; Osterberg & Blaschke, 2005).

Given the burden that non-adherence places on both patients and the healthcare system, it is understandable that considerable effort has been devoted to interventions aimed at addressing this issue. Consistent with the complex aetiology of non-adherence, these interventions are themselves complex and diverse, varying in terms of target population (e.g., patients with cancer, diabetes, or cardiovascular disease), delivery method (e.g., in-person, online/eHealth tools, written materials), interventionists (e.g., pharmacists, nurses, general practitioners), intervention content (e.g., reminders, educational resources, behavioural feedback, interactive components), and whether or not they are grounded in theory (Anderson et al., 2020; Conn & Ruppar, 2017; Kini & Ho, 2018; Wilhelmsen & Eriksson, 2019).

An effort to synthesise the existing literature was made by Conn and Ruppar (Conn & Ruppar, 2017), who conducted a systematic review and meta-analysis of 771 adherence interventions. They reported that habit-based interventions, focusing on behavioural aspects (e.g., prompts to take medications, self-administration practice, special packaging and labelling, behavioural contracts, self-monitoring of adherence), were more effective in improving patients' adherence than those targeting cognitive aspects (e.g., modifying knowledge, beliefs, or attitudes). Furthermore, in-person interventions were found to be more effective than those delivered remotely. Interestingly, interventions delivered by pharmacists were the most effective; this finding is also supported by an overview of systematic reviews, where pharmacists and nurses were identified as the most effective interventionists compared to general practitioners (Wilhelmsen & Eriksson, 2019).

Another overview of 25 high-quality systematic reviews identified 17 categories of medication adherence interventions, among which simplifying dosing regimens, electronic reminders, patient education, and financial incentives or reduced out-of-

pocket costs were associated with modest but positive effects on medication adherence (Anderson et al., 2020).

Although such synthesis efforts are commendable and valuable, they are subject to several important limitations. Besides the considerable heterogeneity in diseases, medications, outcomes, and interventions observed across the reviewed studies, one of the main challenges is the difficulty in categorising the various interventions. As previously mentioned, interventions can differ across multiple dimensions (e.g., interventionists, outcomes, contents, mode of delivery), and different researchers may categorise them in different ways. Some categories may also overlap, or may be too broad, too narrow, or insufficiently described. This issue could be at least partially addressed by adopting an established classification framework, such as the Behaviour Change Technique Ontology (BCTO, (Marques et al., 2023)), which will be explained and discussed in detail in Chapter 2. However, none of the cited works employed such a framework. Furthermore, these systematic reviews and meta-analyses are limited by their general focus, as opposed to a disease-specific one, which may result in a failure to capture important disease-specific differences in the effectiveness of interventions. Moreover, when interpreting the results of these reviews and meta-analyses, it is important to acknowledge that the reported effect sizes are generally modest (for instance, the previously cited meta-analysis by Conn & Ruppar reported a standardised mean difference effect size of 0.290 across 771 adherence intervention studies), the quality of the included studies is often low, and the findings may be affected by various forms of bias, such as publication bias and selection bias (Anderson et al., 2020; Conn & Ruppar, 2017).

Nonetheless, these works provide a valuable foundation for intervention designers, clinicians, and researchers to build upon in developing future interventions and advancing research efforts. The findings underscore the necessity of addressing the multifactorial and complex nature of adherence in order to achieve meaningful improvements. It is not only essential to consider interventions that have demonstrated effectiveness, but also to account for what is feasible and available within specific clinical settings, ensuring that interventions can be realistically implemented in real-world contexts rather than being limited to controlled trial environments (Kini & Ho, 2018).

In conclusion, the picture outlined highlights the need for further research in the field of medication adherence. This work aims to contribute to that effort by specifically addressing medication adherence in the context of breast cancer (BC).

Therefore, having provided a general overview of the issue of non-adherence, we now turn to its specific implications for BC patients. In the following section, after briefly

outlining the main characteristics of this disease, we will revisit the key themes introduced earlier, examining them more closely through the lens of this specific patient population.

1.2 Breast cancer

The term "cancer" refers to a group of diseases characterized by the abnormal and uncontrolled multiplication of altered cells, with the potential to spread in other parts of the body. Cancer is the second leading cause of death worldwide, with an estimated 10 millions deaths and over 19 millions new cases in 2020 alone. Worldwide, BC is the most commonly diagnosed cancer, with over 2 millions new cases in 2020 alone (Ferlay et al., 2021; Wu et al., 2024). Metastatic breast cancer (mBC), also referred to as stage IV or advanced BC, occurs when cancer cells spread beyond the breast and regional lymph nodes to distant organs, most commonly the bones, lungs, liver, and brain (Hooper J. et al., 2024). It accounts for the majority of BC-related deaths. Despite the excellent prognosis associated with early-stage BC, where 5-year survival rates can reach up to 99%, this drops to around 30% for patients with metastatic disease. Notably, it is estimated that approximately 25-30% of women initially diagnosed with early-stage BC will eventually progress to the metastatic stage (Hooper J. et al., 2024).

Considering its immunohistochemical profile, BC is classified into four main subtypes: luminal A, luminal B, HER2-positive, and triple-negative (Orrantia-Borunda et al., 2022). These four subtypes are defined by the expression patterns of oestrogen receptors (ER), progesterone receptors (PR), and the human epidermal growth factor receptor 2 (HER2). *Luminal A* BC is hormone receptor-positive (ER and/or PR) and HER2-negative. It generally responds well to endocrine therapy and is associated with a favourable prognosis. The luminal A subtype accounts for approximately 30-40% of all invasive BCs. *Luminal B* BC is similar to luminal A in being hormone receptor-positive, but it differs by showing a higher Ki-67 proliferation index and, in some cases HER2-positivity. The elevated Ki-67 is associated with increased cell proliferation and a worse prognosis compared to luminal A. The luminal B subtype accounts for approximately 20-30% of all invasive BCs. The *HER2-positive* subtype is characterized by overexpression of HER2. Although it tends to be more aggressive than luminal subtypes, the introduction of HER2-targeted therapies has significantly improved its prognosis. The HER2-positive subtype accounts for approximately 12-20% of all invasive BCs. Finally, the *triple-negative* subtype is ER-negative, PR-negative, and HER2-negative. It is generally highly aggressive and proliferative, and, due to the lack of therapeutic targets, does not respond to either endocrine therapy nor to HER2-

targeted treatments. The triple-negative subtype accounts for approximately 15-20% of all invasive BCs (Fragomeni et al., 2018; Orrantia-Borunda et al., 2022).

BC treatment may include local approaches, such as surgery and radiotherapy, and systemic therapies, including chemotherapy, endocrine therapy, targeted therapy, and immunotherapy. Treatment selection depends on tumour molecular subtypes and stage. Hormone receptor-positive BCs are typically treated with endocrine therapy (e.g., tamoxifen or aromatase inhibitors), sometimes combined with targeted agents. In advanced hormone receptor-positive disease, the standard regimen consists of aromatase inhibitors plus cyclin-dependent kinase 4/6 inhibitors. HER2-positive BCs are typically treated with chemotherapy in combination with agents that specifically target HER2 (e.g., trastuzumab and pertuzumab). Finally, triple-negative BCs are particularly difficult to treat, as they lack specific therapeutic targets. Depending on tumour characteristics, they may be treated with immunotherapy in combination with chemotherapy, or with a specific class of targeted agents known as PARP inhibitors (Xiong et al., 2025).

Notably for our topic, several systemic treatments are commonly administered orally. In such cases, responsibility for correct use falls largely on the patients, who must remember to take their medication as prescribed and manage its administration independently. This shift in responsibility introduces the risk of non-adherence, a phenomenon frequently observed in this patient population (Murphy et al., 2012; Yussof et al., 2022).

1.2.1 Non-adherence in breast cancer

Non-adherence is a particularly important issue in BC, especially with regard to endocrine therapy, which is often administered orally. For this reason, the majority of research in this field has focused on adherence to this class of medication.

Endocrine therapy (also known as hormone therapy) is commonly prescribed either after surgery (as adjuvant therapy) or, in some cases, before surgery (as neoadjuvant therapy) for the treatment of hormone receptor-positive BCs, which account for more than two-thirds of all BC cases. This therapy works either by reducing oestrogen levels in the body (e.g., aromatase inhibitors) or by blocking ER, thereby preventing these hormones from stimulating tumour growth (e.g., tamoxifen). Endocrine treatment is usually prescribed for a minimum of five years, and may be extended in patients at higher risk of recurrence (Chaput & Sumar, 2022). This treatment is generally well tolerated; however, it is often associated with a range of unpleasant side effects resulting from prolonged oestrogen deprivation, including musculoskeletal symptoms (e.g., joint and muscle pain), gynaecological symptoms (e.g., hot flashes, night sweats, vaginal dryness), osteoporosis, and fatigue (Balazard et al., 2023; Nabieva &

Fasching, 2021). These spectrum of symptoms is among the factors that negatively impact adherence in BC patients (Todd et al., 2024; Yussof et al., 2022).

Endocrine therapy non-adherence rates reported in the literature vary considerably, depending on several factors such as the time of assessment, the measurement method, the population studied, and the type of medication. A systematic review of 21 studies found that the prevalence of adherence ranged from 41% to 100%. When focusing on adherence measured at least four years after treatment initiation, the reported prevalence ranged from 41% to 72%. Additionally, the prevalence of treatment discontinuation by the end of the fifth year ranged from 31% to 73% (Murphy et al., 2012). A more recent systematic review of 26 studies reported adherence rates five years after treatment initiation ranging from 33.3% to 88.6%, with an average decline of 25.5% between the first and fifth year of therapy (Yussof et al., 2022). Although reported adherence rates vary widely, the findings consistently highlight a significant issue of non-adherence among BC patients, thereby justifying the considerable amount of research devoted to this topic.

Evidence indicates that non-adherence to endocrine therapy is significantly associated with adverse clinical outcomes, such as higher rates of disease recurrence and progression, ultimately leading to a poorer prognosis (Inotai et al., 2021; Nabieva & Fasching, 2021; Pistilli et al., 2020). A systematic review identified studies evaluating the impact of non-adherence to endocrine therapy on hard clinical outcomes using real-world data. Across the 12 studies included, there was strong evidence that non-adherence is associated with an increased risk of distant metastasis, higher likelihood of disease recurrence, reduced disease-free survival, and increased mortality (Inotai et al., 2021).

1.2.2 Non-adherence in metastatic breast cancer

While the phenomenon of non-adherence has been primarily studied in early-stage BC, considerably less data are available for patients with metastatic disease, both in terms of understanding the extent of the phenomenon in this population and in the development of interventions tailored to address it (Pezzolato, Marzorati, et al., 2023). This gap reflects the overall lower level of attention devoted to mBC, a setting in which research and healthcare policies have historically prioritised early-stage forms of the disease (Hooper J. et al., 2024; Thrift-Perry et al., 2018). In an effort to at least partially address this gap in the literature on medication non-adherence, two original studies presented in this thesis focus specifically on individuals diagnosed with mBC. A detailed account of these studies is provided in Chapter 4.

Among the few studies investigating non-adherence in mBC patients, some have reported relatively higher adherence rates within this clinical population (Conley et al., 2022; Komatsu et al., 2020). One possible explanation is that mBC patients may hold different representations of their treatment. In particular, drawing on the Necessity-Concerns Framework (NCF – for a description of this model the reader is referred to Chapter 2), it can be hypothesised that patients in the metastatic stage perceive their medication as more essential, often viewing it as their only opportunity to extend life or maintain its quality, and therefore adhere to treatment more persistently than many early-stage patients. This hypothesis was preliminary explored in Study 5 and will be discussed in depth in Chapter 4.

Nonetheless, suboptimal adherence has also been documented: for instance, the 22% of the mBC patients assessed by Delea et al. had rates of adherence to lapatinib (i.e., an oral targeted agent) lower than 80% (Delea et al., 2014). Further, a study by Husinka et al. reported rates of adherence to specific oral targeted agents (cyclin-dependent kinase 4/6 inhibitors) ranging from 67% to 81% (Husinka et al., 2021); according to Yerrapragada et al. 40% was non-adherent with tamoxifen (a commonly prescribed endocrine oral therapy) during the first year from prescription (Yerrapragada et al., 2021). The presence of contrasting results in the few studies exploring adherence rates among advanced and metastatic cancer patients makes it necessary to explore this phenomenon also in this population. Accordingly, one of the main objectives of the doctoral project presented here is to contribute to a deeper understanding of adherence within this clinically and psychologically distinct population.

Before turning to this subgroup in Chapter 4, the thesis first examines non-adherence in BC more broadly, where the evidence base is far more extensive. This wider review synthesises and organises current findings, across determinants, predictive models, and intervention strategies, to clarify the state of the art and provide the foundation for the subsequent focus on mBC.

1.3 The determinants of non-adherence

Given the magnitude of the phenomenon and its negative impact on clinical outcomes, numerous studies have been conducted to investigate the underlying factors contributing to non-adherence. Consistent with its multifaceted nature, these studies have yielded heterogeneous and sometimes conflicting findings, identifying a broad range of associated factors. Recently, Todd et al. conducted an umbrella review to identify the determinants of adherence to adjuvant endocrine therapy in BC patients (Todd et al., 2024). The authors analysed 17 systematic reviews, identifying factors

that span all five of the WHO's categories of non-adherence: socioeconomic factors, healthcare team/health system-related factors, condition-related factors, therapy-related factors, and patient-related factors. Among the included systematic reviews, the factors most consistently associated with non-adherence were lower perceived necessity of endocrine therapy, greater concerns about treatment, and patients' perceptions of the therapy's pros and cons (patient-related factors); a poor relationship, interaction, or communication with HCP (healthcare team-related factors); and a lack of social, practical, or emotional support (socioeconomic factors).

Concerning therapy-related factors, the majority of reviews indicated that treatment side effects were associated with non-adherence. In addition, poor management of side effects, lack of coping strategies, and higher treatment costs were also reported as contributing factors.

The evidence regarding the association between non-adherence and condition-related factors, such as the presence of comorbidities, disease severity, a history of previous anti-cancer treatment, mental health conditions, and the use of psychotropic medications, was inconsistent, with some reviews reporting significant associations and others reporting mixed or neutral findings.

Other factors reported as contributing to patients non-adherence in some of the analysed reviews included negative emotions or attitudes toward the therapy, limited knowledge about BC and its treatment, low self-efficacy, forgetfulness, being at the extreme of the age spectrum, and being unmarried (Todd et al., 2024).

The numerous and diverse determinants identified in the scientific literature highlight the complexity of non-adherence in BC care. Consequently, effective interventions should adopt a multidimensional approach, addressing the various contributing factors and ideally involving a multidisciplinary team of HCPs. In parallel, predictive models can use these determinants for practical purposes, such as identifying patients at higher risk of non-adherence and informing more targeted and timely interventions.

1.3.1 Predictive models

The economic and human resources available for supporting BC patients are often insufficient to meet the growing and complex needs of this population. Therefore, it becomes crucial to allocate them as efficiently as possible. This requires identifying those patients who are most likely to benefit from interventions aimed at improving treatment adherence. In this context, the development of reliable predictive models is particularly important.

Predictive modelling is a process that uses mathematical or computational analyses to forecast outcomes or events (Toma & Wei, 2023). In medicine and healthcare, predictive models have been successfully applied in several areas, including supporting

clinical decision-making, predicting disease progression, and identifying high-risk patients. However, the development and deployment of such models present several challenges. These include limited data availability, variability in data quality, and the need to manage sensitive patient information in compliance with data protection regulations and to rigorously validate the resulting models. (Toma & Wei, 2023). An additional, often underestimated challenge lies in translating predictive models from development to real-world clinical practice. This process involves integrating them into existing workflows, fostering clinician trust through training, and continuously monitoring model performance in clinical settings (Seneviratne et al., 2020).

Several predicting models have been developed to estimate medication adherence among BC patients. This thesis presents two reviews specifically focused on this population: a scoping review of predictive models for medication adherence (Study 2), and a systematic review specifically addressing models that incorporate machine learning (ML) techniques (Study 3). These reviews are comprehensively discussed in Chapter 3.

1.4 Interventions to support breast cancer patients adherence

In this introductory chapter, we have provided an overview of the phenomenon of non-adherence to oral therapies in BC, outlining its key characteristics, estimated dimensions, clinical consequences, associated factors, and current approaches to predicting its occurrence. The body of knowledge presented here, along with ongoing and past research efforts, forms the groundwork for the development, evaluation, and implementation of targeted interventions aimed at improving adherence among BC patients. The importance of these efforts is underscored by the WHO, which has reiterated that enhancing patient adherence may yield greater improvements in health outcomes than the development of new medical treatments (World Health Organization, 2003). After all, no therapy can be effective if it is not taken as prescribed.

A wide range of strategies have been explored to enhance adherence to oral medications, differing substantially in both design and delivery (Pezzolato, Marzorati, et al., 2023). These include educational resources, digital tools such as mobile apps delivering reminders, and multidisciplinary support interventions involving healthcare professionals like nurses, dietitians, and psychologists. Nevertheless, the literature indicates that, despite the breadth of these efforts, their effectiveness remains limited, with only modest improvements observed (Finitsis et al., 2019; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016; Nieuwlaat et al., 2014; Pezzolato, Marzorati, et al., 2023).

Given the variety of studies conducted on this topic, a systematic review (Study 1)

was conducted as the first step of this PhD project to examine interventions aimed at supporting adherence among BC patients (Pezzolato, Marzorati, et al., 2023). Published in 2023, the review includes 36 studies released between 2009 and 2022, each describing an intervention targeting medication adherence in this population. Every intervention was analysed using the Behaviour Change Technique Taxonomy (BCTT) (Michie et al., 2013) to identify the specific techniques employed and their associated outcomes. This review will be presented and discussed in detail in Chapter 3.

Artificial intelligence (AI) has the potential to make a substantial contribution both in predictive modelling and in interventions aimed at supporting BC patients throughout their care. Its role in this field will be introduced in the following section and examined in greater depth in the context of Study 3 (see Chapter 3).

1.5 Artificial intelligence

AI is a rapidly growing field and its applications are being increasingly adopted across various domains. Healthcare is no exception: researchers and professionals are actively exploring its potential in numerous areas, including medication adherence (Bekbolatova et al., 2024; Reis et al., 2025; Salama et al., 2024). One of the studies presented in this PhD thesis (Study 3) is a systematic review of AI applications in the context of medication adherence among BC patients. For this reason, a brief introduction to the topic of AI is provided.

Defining AI remains challenging. Although several definitions have been proposed over time, a universally accepted definition is still lacking. Some are criticized for being too broad, while others are considered too narrow or restrictive (Sheikh et al., 2023). For the purposes of this work, we adopt the definition proposed by the European Commission, which offers a well-balanced compromise between overly broad and overly narrow interpretations. According to this definition, AI refers to "systems that display intelligent behaviour by analysing their environment and taking actions – with some degree of autonomy – to achieve specific goals" (Communication from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions on Artificial Intelligence for Europe, 2018, p. 1). Among the systems that fall under this definition, we can further classify and characterise the main subtypes, including ML, natural language processing (NLP), generative AI, and computer vision.

ML broadly refers to a set of algorithms capable of learning from data, identifying patterns, and generating predictions or supporting decision-making. The field of ML has advanced significantly over the past decades, particularly with the emergence of *deep learning* (DL), a subset of ML inspired by the structure and function of neural networks (Arigo et al., 2024; Sheikh et al., 2023; Zhang et al., 2023).

NLP encompasses a set of techniques, typically applied to text or spoken language, used to automatically process, understand, and sometimes generate human language. Among the various applications of NLP, the development of large language models (LLMs - e.g., ChatGPT) represents one of the most significant achievements (Arigo et al., 2024; Zhou et al., 2022).

Generative AI refers to AI technologies designed to produce contents in various formats, such as text, images, or audio. LLMs are among the most prominent examples of generative AI (Arigo et al., 2024; P. Yu et al., 2023).

Finally, *computer vision* involves the collection of data through sensors or cameras and its processing using ML or DL algorithms, with the aim of identifying, classifying, and interpreting visual content (Arigo et al., 2024; Lindroth et al., 2024). As examples, computer vision has been used to diagnose skin cancer analysing skin lesions' images (Akilandasowmya et al., 2024) and to identify food in order to deliver personalised information to the users participating in an intervention (Chew et al., 2024).

These subtypes are not entirely distinct and often intersect. ML provides the core framework underlying many applications in NLP, generative AI, and computer vision. Generative AI typically relies on DL models, and in the case of language-based systems, also on NLP techniques. Computer vision, likewise, is largely based on DL (Arigo et al., 2024).

1.5.1 Artificial intelligence in breast cancer care

The AI technologies listed above have all been applied in healthcare. In line with the focus of this work, we will briefly present some of their applications in the field of BC.

AI applications in BC span a wide range of domains, including drug discovery, early and accurate diagnosis, personalised treatment planning, and remote patient monitoring, management, and supportive care (Bhattacharya et al., 2024; Uchikov et al., 2024). First of all, in the context of drug discovery, ML techniques are employed to accelerate the identification of novel drug candidates, support the design of new molecules and optimise their screening (Bhattacharya et al., 2024; Sliwoski et al., 2014). For diagnostic purposes, computer vision techniques based on DL neural networks are used for the analysis of medical imaging, including mammograms, magnetic resonance imaging, and pathology slides. These systems can identify patterns or anomalies that may not be perceived by human pathologists, thereby

reducing the risk of human error. As a result, they enhance diagnostic accuracy, sensitivity, and specificity, and support earlier detection, potentially enabling timely intervention and improving patient outcomes (Bhattacharya et al., 2024; Uchikov et al., 2024). Furthermore, for personalized treatment planning, ML algorithms have been used to integrate and process heterogeneous patient data, such as genetic, clinical, and demographic information, in order to predict outcomes, including treatment response. As a result, these technologies can support clinical decision-making and enable more accurate patient stratification, ultimately leading to better therapeutic results (Bhattacharya et al., 2024; Uchikov et al., 2024). Finally, AI-powered tools can support both patients and HCPs through eHealth platforms and wearable devices that enable remote monitoring. These technologies facilitate symptom tracking, personalised care management, tailored recommendations based on real-time patient data, timely communication, and patient navigation (Bhattacharya et al., 2024).

Overall, these AI applications are driving significant advancements in BC care; however, alongside these improvements, they also present important challenges that must be addressed (Bhattacharya et al., 2024; Uchikov et al., 2024). These include the variability and heterogeneity of healthcare data, ethical and legal concerns, and the limited real-world validation of many AI models. The so-called "black-box" nature of DL systems raises issues of transparency and explainability. In addition, there is a risk of clinician "de-skilling" if excessive reliance is placed on such technologies. Furthermore, the integration of these tools into clinical workflows requires appropriate infrastructure, clinician training, and the establishment of clear protocols to ensure safe and effective use (Bhattacharya et al., 2024; Khan et al., 2024; Seneviratne et al., 2020; Uchikov et al., 2024). These challenges will be discussed more thoroughly in in the context of Study 3 (see Chapter 3).

1.5.2 Artificial intelligence and non-adherence

As mentioned above, AI technologies have also been employed to address the issue of medication non-adherence (Reis et al., 2025). In particular, ML and DL predictive models are being developed to forecast patients' medication-taking behaviours, with the aim of identifying individuals at high risk and enabling timely interventions (Masiero et al., 2023; Rinder et al., 2024).

While one of the systematic reviews presented in this thesis focuses specifically on AI applications for medication adherence in BC patients and will be discussed in detail in Chapter 3, it is worth briefly mentioning here a recent review by Reis et al. (Reis et al., 2025), which analysed studies on AI-based tools to improve medication adherence

across clinical populations (e.g., individuals suffering from schizophrenia, type 2 diabetes, hypertension) without focusing on any specific condition.

The authors synthesised the findings of seven original studies: four tested AI tools in real-world settings, while three used simulation-based approaches. The AI solutions proposed included mobile applications, a LLM-based voice generator, and systems that employ and integrate various devices, such as smart pill bottles, sensors, cameras, and smart home TV platforms, to collect data and deliver interactive functions aimed at supporting medication adherence. Common functions performed by these AI solutions included real-time patient monitoring, adherence tracking, providing feedback or reminders, and predicting patient adherence. The authors concluded that, although the interventions appeared to improve patient adherence (where a comparison was made, patients exposed to AI-tools showed improvements in adherence ranging from 6.1% to 32.7% compared to those who were not), the evidence supporting the specific contribution of AI remains weak. Indeed, the studies suffered from some methodological limitations and risk of bias, and it was not always possible to separate the effect of AI-based components from the broader patient surveillance strategies in which they were embedded. Despite these limitations, the review offers a valuable overview of the current landscape of AI applications in medication adherence and identify key gaps and opportunities for further research (Reis et al., 2025).

Having introduced the key themes addressed throughout this doctoral project, this introductory chapter concludes with a section outlining the specific objectives that guided the work.

1.6 Objectives

Building on the outlined background, this PhD thesis aims to address the issue of non-adherence to oral medications among BC patients in a thorough and systematic manner. A comprehensive overview of non-adherence in the context of BC has been provided, with a focus on key aspects such as its determinants, the role of predictive models, and the range of interventions proposed to mitigate it. Particular attention has been devoted to the case of mBC, as well as to the potential contribution of AI technologies in enhancing the understanding and management of this issue.

In the following chapters, we will focus on the following open questions: (1) how can patients with BC, and especially those living with metastatic disease, be supported in remaining adherent to their oral therapies? And (2) given the constraints and limited resources of healthcare systems, how can we identify those individuals most in need of targeted interventions or additional support? These open questions will be examined

in depth in light of the existing scientific literature. The original research studies presented in this thesis are intended to enhance current knowledge and contribute to a more comprehensive and integrated understanding of the topic. But first, Chapter 2 will outline the theoretical and methodological foundations of adherence research.

2. Theoretical background

In this chapter, the theoretical and methodological foundations of this PhD thesis will be thoroughly outlined and discussed. We will begin by introducing the field of health psychology, which provide the conceptual framework for the entire work. Particular attention will be given to the issue of behaviour change, due to its significant impact on the health of both the general population and individuals affected by cancer. The main theoretical models developed over time within this discipline to understand and explain health behaviours will be outlined, along with their application to the specific issue of medication adherence. Furthermore, key efforts to render the complex domain of behaviour change interventions more accessible to scientific investigation will be examined, with a particular focus on the development of the BCTO (Marques et al., 2023) and its evolution from the earlier BCTT (Michie et al., 2013).

The chapter will also introduce factorial designs, an increasingly relevant approach for the evaluation and optimisation of complex interventions. By enabling researchers to assess the individual contribution of specific components within multifaceted interventions, such as those targeting behaviour change, as well as their potential synergies or interferences, this methodology offers a valuable framework for optimisation studies. In these studies, interventions components and their interactions are systematically evaluated to determine whether, and in which combination, they should be tested in fully powered randomised controlled trials. The characteristics of factorial designs make them particularly well-suited for assessing complex interventions aimed at supporting medication adherence, as explored in this thesis.

2.1 Health psychology

Health psychology is the branch of psychology that examines how psychological and behavioural processes influence health, illness, and healthcare (Johnston & Dixon, 2008). More specifically, this discipline investigates the role of psychological and behavioural factors in maintaining health, as well as in the onset, development, and rehabilitation of illness. It also encompasses the development of interventions aimed at promoting health or supporting patients in their recovery from illness (Guangyu & Xinghua, 2024). Health psychology is closely related to behavioural medicine, to the extent that their aims and definitions substantially overlap. The key distinction lies in the fact that, while health psychology is a subfield within psychology, behavioural medicine is inherently multidisciplinary (Guangyu & Xinghua, 2024; Kaplan, 2009).

The origins of health psychology can be traced back to 1969, when William Schofield published a report for the American Psychological Association (APA) titled “The Role of

Psychology in the Delivery of Health Services" (Schofield, 1969) In this report, the author emphasised the need for psychology to broaden its focus beyond mental health to include general health more broadly. He advocated for the study of the "psychology of physical illnesses" and called for the training of "medical psychologists" with specialised expertise in this emerging field. Following this report, an APA task force on the role of psychology in health research was established in 1973. This ultimately led to the foundation of the Society for Health Psychology in 1978, which marked the official birth of health psychology as a distinct field within psychology (Guangyu & Xinghua, 2024).

Today, health psychology has grown significantly; its division within the APA is now among the largest, and one of its dedicated journal, "Health Psychology," ranks among the most widely subscribed empirical journals in the field (Kaplan, 2009).

Health psychology explores a wide range of topics that can be broadly divided into four main research areas: (1) promoting and maintaining health, for example by encouraging healthy habits such as following a balanced diet or engaging in regular physical activity; (2) preventing disease and supporting treatment, for example helping people manage occupational stress or adhere to their medication; (3) understanding the aetiology of health, disease, and dysfunction, for example by exploring how psychosocial factors are connected to health and how they may contribute to the onset and progression of disease; and (4) improving healthcare systems and policies, for example by studying how system or societal factors impact people's health, and how addressing these could lead to better outcomes for entire populations (Guangyu & Xinghua, 2024). It is important to note that these domains are not only the focus of research, but also represent areas of practical engagement, as health psychologists are actively involved in educational activities and clinical services aimed at addressing these same behaviours and issues (Kaplan, 2009).

As this brief overview of health psychology's research domains suggests, health behaviour change is a central focus of both research and intervention efforts within the discipline. Among the behaviours shown to significantly impact health and therefore at the core of health psychology's interest are smoking, alcohol consumption, physical activity, and dietary habits (Johnston et al., 2011; Johnston & Dixon, 2008; Kaplan, 2009; Leventhal et al., 2008). Medication-taking behaviour and the issue of non-adherence have also received considerable attention from health psychologists, as will be explored in detail in the following sections of this thesis. But first, we will explore the theoretical models developed within the field of health psychology that form the conceptual framework for understanding and explaining behaviour change.

2.1.1 Health behaviour change models

Several models have been proposed to understand and explain the factors that influence whether or not a specific health behaviour, such as quitting smoking, participating in a screening program, or adhering to prescribed medication, is adopted. Because the development of such models represents a cornerstone in the scientific study of medication adherence, it is important to provide an introductory overview of the main frameworks that have emerged within health psychology research. The explanatory value and practical relevance of each model in relation to non-adherence will be assessed according to three key criteria: (1) its comprehensiveness, meaning the extent to which it captures the range of factors that influence medication-taking behaviour, (2) its explanatory power in accounting for differences in adherence behaviour, and (3) its capacity to inform the development of interventions aimed at improving adherence. For the purposes of this thesis, only the models most relevant to our focus have been selected, while additional frameworks can be found in the referenced literature (Armitage & Conner, 2000; Horne & Weinman, 1998; Munro et al., 2007).

Social cognitive models focus on cognitive variables, such as expectations, beliefs, and attitudes, as proximal determinants of behaviour. Such variables can directly influence the adoption of behaviour or mediate the impact of other factors, thereby providing a conceptual foundation for understanding behaviour (Conner & Norman, 1998; Horne & Weinman, 1998). Therefore, the relevance of social cognitive models to the present thesis lies in the fact that they identify modifiable psychological variables that could potentially be targeted by behaviour change interventions, including those designed to promote medication adherence. While sociodemographic factors are largely fixed, cognitive variable can typically be influenced through well-designed interventions (Armitage & Conner, 2000). For example, many adherence-enhancing programmes that provide patients with educational material in different formats can be interpreted as targeting these variables: by offering new knowledge and stimulating reflection, such interventions may alter patients' beliefs and representations about their illness and treatment, thereby fostering better adherence.
We will begin by briefly outlining the health belief model (HBM), the theory of reasoned action (TRA), and the theory of planned behaviour (TPB).

The HBM was originally developed in 1966 to understand the barriers that prevent individuals from adopting disease prevention measures and participating in screening tests (Horne & Weinman, 1998; Jones et al., 2014; Rosenstock, 1974). The original model posits that the likelihood of an individual engaging in a specific health behaviour

depends on their beliefs about the risk of the disease, namely, their perceived susceptibility and perceived severity, as well as their assessment of the perceived barriers and benefits associated with that behaviour. According to the HBM, the greater the perceived risk and the more the perceived benefits outweigh the barriers, the more likely is the behaviour to occur. Subsequent revisions of the model have incorporated additional elements, such as general health motivations, general orientation toward medicine, and the need for a cue to action to initiate the behaviour (Horne & Weinman, 1998).

The HBM has been widely applied to the study of health-related behaviour, and medication adherence is no exception. Within the systematic review on adherence interventions in BC patients (Pezzolato, Marzorati, et al., 2023) presented in Chapter 3 (Study 1), two of the included interventions were partially informed by this model. In particular, Ell et al. (Ell et al., 2009) compared the provision of written information with a telephone-based patient navigation programme in a randomised controlled trial. The authors described the navigation programme as consistent with the HBM, since it was designed to enhance participants' knowledge and attitudes while simultaneously addressing perceived barriers to adherence. Both experimental groups achieved high adherence rates, and the HBM-informed intervention did not demonstrate superior outcomes compared with the written information condition. Similarly, Yanez et al. (Yanez et al., 2022) designed an online mindfulness-based programme that also incorporated HBM-informed elements, including educational content on endocrine therapy and strategies to manage side effects. Unlike the previous trial, this work was presented as a usability study alongside the protocol for a randomised controlled trial, therefore the evidence on its effectiveness is not yet available.

In addition, a further 19 studies applying the HBM to interventions aimed at enhancing adherence were examined in another systematic review (Jones et al., 2014). The authors, however, found only limited evidence of effectiveness, reporting no consistent association between the model's constructs and adherence outcomes. These results appear to challenge the model's validity in relation to the second and third assessment criteria outlined above, namely, its explanatory power in accounting for changes in behaviour and its ability to guide the development of effective adherence-enhancing interventions.

Moreover, while the HBM has the merit of highlighting the importance of some cognitive factors involved in health behaviours, it also presents some relevant limitations. Some of the criticisms directed at this model concern its oversimplification of health-related constructs into broad categories such as "barriers" and "benefits," which may fail to capture more nuanced underlying beliefs. Additionally, the model tends to frame health behaviours as the outcome of a one-time, rational decision

based on a conscious evaluation of benefits and barriers. However, research suggests that such behaviours are often also driven by deeper, less rational processes that the model fails to adequately capture (Hagger, 2025; Williams et al., 2019). As such, it does not fully meet the comprehensiveness criterion, as it fails to encompass the full range of factors that may influence adherence. Moreover, the model has been criticised for lacking a construct related to intentions, thereby leaving a gap between individuals' health beliefs and their actual behaviours (Horne & Weinman, 1998; Jones et al., 2014). This limitation is overcome in the TRA, which introduces the concept of behavioural intention as a key determinant of action.

The TRA originated from research on how attitudes translate into behaviours, initially outside the context of health. However, it was later widely applied to the study of health-related behaviour, including medication adherence (Holmes et al., 2014; Horne & Weinman, 1998). As previously mentioned, this theory introduces the construct of intention as the key link between attitudes and behaviours. Therefore, the TRA proposes a linear sequence in which behaviour is determined by intentions, which in turn are shaped by two main factors: attitudes, based on beliefs about the possible outcomes of the behaviour and the value assigned to those outcomes, and subjective norms, reflecting beliefs about others' expectations and the motivation to comply with them (Horne & Weinman, 1998).

The TRA does not account for behaviours that fall outside conscious control, nor does it consider the influence of past behaviours, thereby again failing to satisfy the comprehensiveness criterion (the remaining two criteria will be addressed in relation to the next model, which represents an extension of the TRA). To address these limitations, its authors introduced the construct of perceived behavioural control, leading to the development of what they called TPB (Horne & Weinman, 1998; Munro et al., 2007). Perceived behavioural control refers to the extent to which individuals believe they can exert control over their own behaviour. It is shaped by control beliefs and encompasses various factors, including emotions, past behaviours, experiences, behavioural skills, and external circumstances. This construct largely overlaps with the construct of self-efficacy developed by Albert Bandura (Bandura, 1982).
One of the adherence interventions for BC reviewed in Study 1 (Pezzolato, Marzorati, et al., 2023) drew on the TPB: Moon et al. (Moon et al., 2019) developed a self-directed psychoeducational manual organised into four weekly modules addressing different aspects of adherence to endocrine therapy. The manual was informed by both the common-sense model of self-regulation (CSM; see below) and the TPB; some sections were explicitly designed to target core TPB constructs, such as strengthening

intentions to take medication as prescribed, fostering more positive attitudes toward treatment, and enhancing perceived behavioural control (Moon, 2017; Moon et al., 2019). The study reported that the intervention was both feasible and acceptable to patients; however, as a single-arm trial with a relatively small sample, it was not sufficient to establish its efficacy. In addition, the TPB's efficacy in predicting medication adherence was evaluated in a systematic review of 27 studies from Rich et al. (Rich et al., 2015). The authors found that the theory's constructs accounted for 33% of the variance in the intention to adhere to medication and 9% of the variance in actual adherence behaviour. However, although this findings suggest that this theory can at least partially account for medication non-adherence, thereby partially satisfying our explanatory power criterion, the small-to-medium effect sizes observed by the authors do not support recommanding it as the sole theoretical framework for predicting adherence or informing intervention design (Rich et al., 2015), thus failing to meet our related criteria. Moreover, although the addition of the construct of perceived behavioural control broadens the range of person-related factors included in this model, it still lacks comprehensiveness, similarly to other cognitive frameworks, as it does not sufficiently account for additional determinants such as socioeconomic, treatment-related, and health system factors.

Social cognitive models, such as those outlined above, have made a significant contribution to health psychology and to the understanding of health behaviour change by highlighting the role of various cognitive factors in shaping health-related behaviours. However, these models have been criticised for placing excessive emphasis on rational volition, thus failing to account for seemingly irrational behaviours, such as delaying cancer treatment or engaging in actions known to be harmful (Horne & Weinman, 1998). As such, they do not meet our comprehensiveness criterion, as discussed above. Similarly, the available evidence does not support these models' capacity to inform the development of effective adherence interventions, nor their explanatory power (with the sole exception of the TPB, which only partially satisfies this criterion). Another limitation of these models is their static nature, as they fail to account for the dynamic processes involved in health behaviours. In fact, the cognitive factors influencing the initiation of a medical treatment may differ significantly from those required to maintain that treatment over time. An attempt to address this limitation is offered by the so-called stage theories, the most prominent of which is the transtheoretical model (TTM; also known as the stages of change model) (Horne & Weinman, 1998; Munro et al., 2007; Prochaska & Velicer, 1997).

The TTM describes five stages involved in the process of adopting and maintaining a health behaviour. These are: (1) *precontemplation*, when the individual is not yet considering the behaviour—for example, a patient is not thinking about adhering to their medication for various reasons; (2) *contemplation*, when the individual begins to consider engaging in the behaviour—e.g., the patient starts to reflect on the possibility of following the treatment; (3) *preparation*, when the individual intends to take action in the near future—e.g., the patient decides to begin adhering to their medication soon; (4) *action*, when the behaviour is actively initiated—e.g., the patient starts taking their medication regularly; and (5) *maintenance*, when the behaviour is sustained over time—e.g., the patient consistently takes their medication over a full month (Horne & Weinman, 1998; Munro et al., 2007). These stages are not conceived as a linear or uniform progression, but rather as part of a recursive cycle. The process of adopting and maintaining the desired behaviour is characterised by both forward movements through the stages and potential setbacks or relapses, reflecting the dynamic and non-linear nature of behaviour change (Horne & Weinman, 1998; Munro et al., 2007). Ten processes of change (e.g., consciousness raising, helping relationships, reinforcement management) are identified as mechanisms through which individuals can overcome the barriers they face at different stages of behavioural change (Bridle et al., 2005).

The TTM has been widely applied to a range of health behaviour, including smoking cessation, dietary change, physical activity, and medication adherence (Bridle et al., 2005; Imeri et al., 2022). A systematic review of 37 randomised controlled trials addressing seven different health behaviours concluded that there is insufficient evidence to support the effectiveness of interventions based on this model in achieving behaviour change or in facilitating progressing through the proposed stages (Bridle et al., 2005). A more recent systematic review examining the usefulness of the TTM in predicting or improving medication adherence found that only three out of five TTM-based interventions reported positive effects on adherence. The remaining five studies identified associations between TTM stages and medication adherence. However, the authors highlighted the lack of robust evidence and stressed the need for further research (Imeri et al., 2022). An additional consideration, which calls for caution when evaluating this model's explanatory value even in light of Imeri's systematic review, concerns the specific characteristics of the model, particularly its stage definitions. These raise doubts as to whether the associations reported in the included studies truly reflect explanatory validity, or instead represent a redundancy between how adherence is defined and how stages are conceptualised. For instance, it is reasonable to expect that a patient who self-reports being adherent will also report being in the action or maintenance stages, given that these stages are, by definition, those in

which the target behaviour is already being performed or maintained. Therefore, based on the limited available evidence and considering the aspects discussed above, the TTM cannot be regarded as fulfilling either the explanatory value criterion or the criterion relating to its usefulness in guiding effective intervention design. Moreover, as the model does not explicitly address determinants of medication adherence, its comprehensiveness cannot be meaningfully assessed.

Nonetheless, this model presents some relevant strengths, such as its potential to be used to tailor interventions to the specific stage of change at which the patient is situated. Several further limitations have also been highlighted. It has been argued that, due to the inherent complexity of human behaviour, categorising it into discrete stages may be overly simplistic and could limit the scope of behaviour change interventions. Furthermore, critics have pointed out that the model gives insufficient attention to the mechanisms by which individuals move between stages, and to the reasons why some succeed while others do not (Munro et al., 2007). In particular, the factors that support sustained motivation during the maintenance stage remain inadequately addressed (Horne & Weinman, 1998). The next model to be presented attempts to comprehensively address the dynamic interplay of perceptual, behavioural, and cognitive processes involved in patients' self-regulation in response to health threats (Leventhal et al., 2016).

The CSM views patients as active problem-solvers whose health behaviour represents an attempt to move from a perceived current health threat toward a desired future state. The model is characterised by three central elements: the cognitive representations of the health threat, the coping strategies employed to address it, and the appraisal of outcomes. These components interact in a feedback loop, each influencing the others. Under this model, medication-taking behaviour can be viewed as a coping strategy, and the decision to take or forgo prescribed medicine depends on patients' illness representations and their direct symptom experiences. The model's dynamic nature accounts for the possibility that both coping strategies and cognitive representations may be revised following outcomes appraisal (Horne & Weinman, 1998; Jones et al., 2016; Leventhal et al., 2016). For instance, if a patient initiates treatment but experiences worsening symptoms instead of improvement, they may no longer regard the medication as an effective coping strategy and may accordingly revise their illness representations. An important feature of the CSM is that it accounts for the parallel processing of cognitive and emotional elements, thus explaining not only rational behaviours but also seemingly irrational ones driven by emotional responses (Horne & Weinman, 1998). Compared with the models discussed previously, this element represents a meaningful step forward in terms of comprehensiveness.

However, the emphasis remains largely on individual-level determinants, with socioeconomic and health system factors once again overlooked.

The CSM has been widely applied to understand, explain, and modify various health behaviours. In the context of cancer care, it has been used to design interventions aimed at symptom management, enhancing health-related quality of life, improving sexual satisfaction among women diagnosed with BC, and supporting medication adherence (Gu et al., 2024). For instance, the CSM (in combination with the TPB) informed the development of the self-directed psychoeducational manual described earlier (Moon, 2017; Moon et al., 2019) and reviewed in Study 1 (Pezzolato, Marzorati, et al., 2023). A systematic review of CSM-based interventions for adherence identified nine studies, six of which demonstrated effectiveness. However, the fact that only one study reported an effect on illness perception, a central construct of CSM, raises concerns about whether the observed outcome truly support or validate the theoretical model. It remains possible that the interventions were effective due to other factors not directly related to the framework proposed by the CSM (Jones et al., 2016). Therefore, the actual usefulness of this model in informing the design of effective interventions has yet to be demonstrated.

It has also been suggested that the complexity of this model makes its underlying processes difficult to operationalise and test, thereby limiting its practical applicability, and raising doubts about its explanatory validity. This is reflected in the fact that many studies employing the CSM have relied on static correlational designs, which fail to capture the model's dynamic nature and the feedback processes it originally proposed. To overcome this limitation, recent extensions of the model have been introduced to enhance its predictive power and facilitate the empirical testing of its mechanisms (Hagger & Orbell, 2022).

A much simpler framework, specifically developed to study medication adherence, is the NCF (Horne & Weinman, 1999, 2002). While both social cognitive models and the CSM acknowledge the role of patients' beliefs, the NCF focuses more specifically on those considered central to medication adherence, namely beliefs about medicines themselves. These core beliefs are divided into those relating to medicines in general and those concerning specific medications. General beliefs about medicines involve the perception of medicines as inherently harmful and best avoided, and the beliefs about how doctors generally manage and prescribe them. Beliefs about specific medications include perceptions of their necessity for maintaining health and the concerns about their potential adverse effects or long-term harm (Horne & Weinman, 1999).

Beyond being tested independently as a framework for medication adherence (Horne et al., 2013; Horne & Weinman, 1999), the NCF has also been incorporated into the

CSM by adding beliefs about medicines to the CSM's illness representations (Horne & Weinman, 2002). In a study with adults with asthma, this extended CSM formulation showed that treatment perceptions (i.e., necessity and concern beliefs) were stronger predictors of non-adherence than illness perceptions. Illness representations did contribute, but their effects were largely indirect, being mediated by necessity beliefs about the medication.

The authors who developed the NCF also designed and validated the Beliefs about Medicines Questionnaire (BMQ) (Horne et al., 1999), a tool that has been widely adopted to test the frameworks validity and, more broadly, to quantitatively assess patients' beliefs about medicines across various clinical populations. Using this tool, studies have shown that beliefs about medicines account for a greater proportion of the variability in adherence compared to sociodemographic and clinical factors, and that these constructs are significantly associated with medication adherence (Foot et al., 2016; Horne et al., 2013; Horne & Weinman, 1999). Although this framework is clearly limited in terms of comprehensiveness, given its emphasis on a narrow set of highly specific beliefs, its capacity to account for variations in medication adherence is nonetheless supported by robust evidence across multiple clinical conditions, indicating a substantial explanatory value. For what concerns its usefulness in designing effective interventions, the available evidence remains very limited and does not allow drawing firm conclusions. Indeed, the studies exploring NCF-based interventions are few, often incorporate additional components (O'Carroll et al., 2013; Perera et al., 2014), or lack sufficient statistical power to detect meaningful differences in adherence outcomes (Magadza et al., 2009). Furthermore, to our knowledge, no literature review or meta-analysis has yet been conducted to investigate this specific aspect.

The central hypothesis derived from the NCF is that adherence is particularly influenced by beliefs about specific medication, namely, that higher perceived necessity and lower concerns are associated with greater adherence. This simple yet powerful hypothesis has been consistently supported by numerous original studies and meta-analyses (Foot et al., 2016; Horne et al., 2013; Todd et al., 2024). Given the substantial evidence supporting this hypothesis and the simplicity of its assessment, the NCF has been adopted in Study 5 to explain medication adherence in patients with mBC. Using the BMQ, we explored the beliefs of this specific clinical population in terms of perceived necessity and concerns regarding their oral anticancer medication. These findings will be presented in detail in Chapter 4.

All the models outlined thus far have the merit of shedding light on various aspects of health behaviour. They differ in complexity, scope, and the emphasis placed on specific

factors. An interesting attempt to capture the complexity of human behaviour in a simple yet comprehensive system is the Capability, Opportunity, Motivation, and Behaviour (COM-B) model (Michie, van Stralen, et al., 2011). The COM-B model was developed as the core component of the broader Behaviour Change Wheel (BCW) framework, a comprehensive framework aimed at characterising behaviour change interventions and linking their components to an analysis of the target behaviours, thereby guiding the design and implementation of interventions. After a thorough review of existing models, the authors found that none satisfied all three utility criteria they had identified: comprehensiveness, coherence, and connection to an overarching model of behaviour. Therefore, this framework was developed to fulfil all three.

The COM-B model accounts for both internal determinants (physical and psychological) and external elements such as environmental and social factors. As such, it can be reasonably regarded as the most comprehensive framework among those examined in this thesis. It postulates that behaviour results from the interaction of capability, opportunity, and motivation, and that these three components are themselves influenced by behaviour. *Capability* refers to the individual's physical and psychological capacity to engage in a specific behaviour. It includes possessing the necessary knowledge and skills to perform it. *Opportunity* comprises all factors external to the individual, both physical and social, that enable or prompt the behaviour. *Motivation* is broadly defined as the set of brain processes that energise and direct behaviour. It includes both reflective processes, such as conscious decision-making, evaluation, and planning, and automatic processes, such as those involved in habit formation, impulses, and emotional responses (Jackson, Eliasson, & Weinman, 2014; Michie, van Stralen, et al., 2011).

Surrounding the COM-B system, nine intervention functions and seven policy categories complete the BCW, identifying the functions and strategies that can be implemented to influence the specific components of the behavioural model.

The COM-B model has been applied to various health behaviours, including medication adherence. For instance, Jackson et al. identified a set of adherence determinants from three extensive systematic reviews (Jackson, Eliasson, & Weinman, 2014). The authors were able to map all these factors onto one or more COM-B components and to illustrate their dynamic interactions, as well as potential ways to intervene effectively. Notably, the model's comprehensiveness also makes it possible to take into account social influences and habit-related factors, areas where many of the previously discussed models fall short.

More recently, the COM-B model has been applied to synthesise evidence on non-adherence in various contexts, including among patients with cardiovascular diseases (Fang et al., 2025; Mishra et al., 2021; L. G. Park et al., 2023) and type 2 diabetes

(Teo et al., 2025), and in relation to specific treatments such as aspirin intake during pregnancy (Vinogradov et al., 2024) and nicotine replacement therapy (Mersha et al., 2020). Although, to our knowledge, no systematic reviews have specifically examinated adherence-enhancing interventions developed using this approach, it is important to note that the BCW was conceived not only to explain behaviour change but also to support the design of interventions. Its eight-step process guides developers from identifying the determinants of the target behaviour using the COM-B model, to selecting the most appropriate intervention functions and policy strategies to address those determinants. Therefore, while evidence on the effectiveness of adherence interventions built on this framework is currently lacking, its structured and theory-driven methodology suggests strong potential for supporting the systematic development of effective interventions (Matakanye & Grace Tshitangano, 2024; Michie et al., 2014).

The brief overview presented in this section highlights the complexity of studying medication adherence from a scientific perspective. None of the models described can be regarded as sufficient, on their own, to fully explain or predict adherence, nor to guide the development of effective interventions (Holmes et al., 2014). Nevertheless, each contributes valuable insights into the cognitive, affective, and social processes that shape this behaviour and its determinants. For the purposes of this thesis, the NCF was selected as the most suitable framework for characterising medication adherence in patients with mBC within the context of Study 5 (see Chapter 4). Its straightforward operationalisation through the BMQ, combined with its demonstrated explanatory power, make it a particularly appropriate tool for examining how medication beliefs relate to adherence in this clinical group, where, to our knowledge, it has not previously been applied. The results of this investigation will be presented in detail in Chapter 4.

2.2 The Behaviour Change Technique Taxonomy and the Behaviour Change Technique Ontology

The theoretical frameworks discussed so far serve as valuable tools for generating hypotheses then can be tested, thereby improving our understanding of human behaviour. Moreover, they constitute an important foundation for the development of interventions aimed at promoting behavioural change in ways that support individual well-being and public health. However, equal importance must be given to the interventions themselves. A relevant effort to classify and describe the full range of techniques used in behaviour change interventions is represented by the BCTT (Michie et al., 2013) and its more recent development, the BCTO (Marques et al., 2023).

In order to accurately describe a behavioural intervention, it is essential to report both the mode of delivery (i.e., who delivers it, to whom, for how long and how often, and in what context and format) and the content of the intervention itself. The BCTT specifically relates to the latter, providing a standardised framework for specifying the active components of intervention content. These components, referred to as behaviour change techniques (BCTs), are defined as the "observable, replicable, and irreducible component of an intervention" (Michie et al., 2013, p. 82) designed to modify a specific behaviour.

Whereas pharmaceutical interventions are relatively straightforward to describe (typically requiring only the specification of the active compound, dosage, frequency, and duration), behavioural interventions tend to be more complex, often involving multiple interacting components that are less easily standardised or replicated. The techniques employed in such interventions are often poorly defined or described using ambiguous terminology. For instance, a term like "motivational counselling" may appear in the description of an intervention, yet its exact meaning can remain unclear. This lack of standardisation presents challenges not only for intervention design and implementation but also for secondary research, where the extraction and synthesis of data from multiple studies require a common and reliable nomenclature.

To address these challenges, the BCTT was developed via a Delphi method involving international experts in behaviour change. The panel reached consensus on 93 specific BCTs, which were then grouped into 16 hierarchical clusters. The resulting taxonomy offers a shared, standardised language that supports clear reporting, faithful replication, and systematic development and implementation of interventions. Moreover, it enables consistent coding of intervention content in systematic reviews, strengthening the rigour and comparability of evidence across studies (Michie et al., 2013).

The BCTT has been used in more then 5,000 published studies to inform intervention design, support evidence synthesis, and guide the implementation of behaviour change interventions (Marques et al., 2023). It has been applied across a wide range of domains, including interventions targeting childhood obesity (Chakraborty et al., 2022), diabetes management (Presseau et al., 2015), and eHealth interventions for patients with cardiovascular disease (Duff et al., 2017). The same taxonomy was employed in Study 1, a systematic review of interventions aimed at supporting medication adherence among BC patients, to identify the BCTs implemented within those interventions (Pezzolato, Marzorati, et al., 2023).

More recently, user evaluation and feedback highlighted the need to update the BCTT. In particular, revisions were required to improve the clarity of labels and definitions, to add new techniques, and to divide some existing ones (Marques et al., 2023). To meet

these needs, the BCTO was developed through an iterative, multi-step process. This involved synthesising feedback from multiple sources, reviewing published studies and classification systems, and refining labels, definitions, and relationships with input from experts in the field. The first published version of the BCTO includes 281 BCTs, organised into 20 higher-level groups and structured across five hierarchical levels. this expansion not only increased the number of techniques but also marked a fundamental shift from a taxonomy to an ontology. While a taxonomy organises items through hierarchical clustering, an ontology provides a formal framework for defining entities, their classes, and their relationships. Each entity is specified in a precise and complete way that makes it interpretable by both human and computers. This logic-based framework allows for greater comprehensiveness and expressiveness. Importantly, the BCTO enables integration of BCTs with other key components of interventions, such as delivery modes, mechanisms of action, and contextual factors like setting and population. It is also designed to be dynamic, supporting continuous refinement and the addition of new entities and relationships. The BCTO forms part of the broader Behaviour Change Intervention Ontology, which includes ten additional ontologies covering areas such as delivery modes, mechanisms of action, and intervention settings (Marques et al., 2023).

2.3 Factorial design and optimisation studies

To fully address the complexity of behaviour change interventions, such as those targeting medication adherence, another crucial aspect to consider is their appropriate optimisation and evaluation. Traditional designs alone, such as randomised controlled trials, may prove limited or insufficiently effective in accurately assessing the true potential of multi-component interventions. Indeed, these interventions are often delivered as "packages," in which participants in the intervention group receive multiple components simultaneously, making it challenging to determine which specific elements are actually driving any observed changes in behaviour. Testing each component in separate arms would require extremely large sample sizes to ensure sufficient statistical power and, moreover, would not allow for the evaluation of potential interaction effects between components. An increasingly adopted solution to this issue is the use of factorial designs (Arigo et al., 2024; Smith et al., 2023). As this doctoral thesis comprises a full factorial pilot optimisation trial (Study 5, see Chapter 4), this emerging study design is briefly introduced.

In factorial designs, participants can be randomised to receive multiple intervention components, thereby maximising statistical power while simultaneously reducing the required sample size. They can be classified as *full factorial designs*, in which all possible combinations of intervention components are tested across different arms, or

as *fractional factorial designs*, in which only a subset of the most relevant combinations is selected for testing. The latter approach is often preferred when the number of potential combination is high (L. M. Collins et al., 2009). In the case of Study 5, however, a full factorial design was considered more appropriate, as only three components were tested, resulting in eight trial arms covering all possible combinations.

A further advantage of using such designs is the possibility to explore potential synergies or interferences between components and to assess their combined effects. For example, when evaluating a multi-component intervention aimed at supporting adherence, it may emerge that the combination of text message reminders with the delivery of educational material is particularly effective. Conversely, it might be found that a specific component is more effective in promoting adherence when delivered alone rather than in combination with other elements.

The multiphase optimisation strategy framework (Guastaferro & Collins, 2021) assigns a central role to factorial designs. Its overarching aim is to balance intervention effectiveness with the implementation constraints imposed by the need for affordability, scalability, and efficiency. The framework is structured into three phases: development, optimisation, and evaluation. Factorial designs are recommended during the optimisation phase to identify the combinations of intervention components that best align with optimisation objectives. The selected combination is then tested against an appropriate control in a fully powered randomised controlled trial, which remains the gold standard for evaluating intervention effectiveness (Guastaferro & Collins, 2021).

As noted above, a full factorial pilot optimisation trial was carried out within Study 5 (see Chapter 4). The trial investigated patient satisfaction and the perceived usefulness of three intervention components (i.e., educational material, personalised reminders, and behavioural feedback) developed to promote medication adherence among patients with mBC. In addition, the study provided a descriptive exploration of the sample, examining patients' sociodemographics and clinical characteristics, relevant psychological variables, and adherence to oral medication. The detailed results will be presented in Chapter 4.

3. Science builds on previous knowledge: systematic reviews and scoping review

Thus far, we have provided an overview of the main models of health behaviour change developed within the field of health psychology. We have then broadened the discussion to the challenge of promoting behaviour change, an issue at the heart of medication non-adherence, by presenting a comprehensive classification system for BCTs and introducing factorial designs, highlighting their relevance for the optimisation of behaviour change interventions.

Now, we turn to the five studies that form the core of this thesis. In this chapter, we will begin by presenting three reviews conducted to explore the current state of knowledge on key themes related to medication non-adherence among BC patients, providing a foundational understanding of the issue. Each review addresses a distinct yet complementary aspect of the topic:

1. a systematic review of interventions designed to support medication adherence (Pezzolato, Marzorati, et al., 2023),
2. a scoping review of predictive models of non-adherence (Pezzolato, Spada, et al., 2023), and
3. a systematic review exploring the use of AI technologies to predict and support adherence (Pezzolato et al., 2025).

Together, these reviews offer a comprehensive overview of the current state of research on medication adherence in BC, informing the subsequent research presented in the thesis.

3.1 Study 1: A systematic review of interventions supporting adherence among breast cancer patients

The first study is a systematic review examining interventions designed to improve adherence to oral medication in BC patients (Pezzolato, Marzorati, et al., 2023). As mentioned in Chapter 1, a wide range of interventions has been proposed, developed, and tested to support patients with BC throughout their care journey, with the goal of promoting optimal medication adherence. These interventions vary considerably in both approach and content: some have focused on providing educational materials, others on the development of mobile applications offering reminders and additional features. Further strategies have involved the implementation of various support

programmes led by HCPs, such as nurses, dietitians, or psychologists. Despite this diversity of approaches and the increasing number of interventions tested over time, previous systematic reviews (Finitsis et al., 2019; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016) have consistently highlighted that their overall effectiveness remains limited, with improvements often modest and, in many cases, failing to reach statistical significance. The present work seeks to provide an updated and comprehensive overview of the current state of knowledge regarding these interventions.

Consistently with the multifaceted nature of non-adherence, the interventions designed to address it are themselves complex and often include multiple active components intended to promote the target behaviour (i.e., adherence). To analyse and classify the content of each interventions in a systematic and rigorous way, the BCTT was employed (Michie et al., 2013). This consensus-based and reliable framework provides a standardised nomenclature for specifying and reporting the content of complex interventions (Michie, Abraham, et al., 2011; Michie et al., 2013). The choice to use the BCTT rather than the more recent BCTO was due to the fact that the study was conducted prior to the publication of the BCTO (Marques et al., 2023) (for a more detailed description of the BCTT and BCTO, refer to the dedicated section in Chapter 2). Applying the BCTT allowed for a clearer understanding of the key features of the interventions and offered valuable insights for the development of new, more tailored programmes aimed at changing behaviour. While the BCTT has already been successfully employed in both primary studies and systematic reviews focusing on various types of behaviour change interventions (Donovan et al., 2022; Talat et al., 2022; Wright et al., 2022), to the best of our knowledge this was the first (and remains the only) study to apply this framework to a review of interventions specifically targeting adherence to oral therapies in BC.

The decision to include all types of oral anticancer therapies (i.e., endocrine therapy, oral chemotherapy, and targeted therapy) reflects the intention to provide a broad and comprehensive overview, capturing the full range of relevant studies on the topic rather than limiting the focus to endocrine therapy, which has been the primary focus of most previous reviews (Finitsis et al., 2019; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). Similarly, studies were included regardless of BC stage, encompassing both early-stage and advanced patients. In addition, both completed studies and protocols describing the design and development of interventions were considered, in order to offer a thorough picture of the existing landscape and ongoing research in this area.

3.1.1 Aims of the study

The main objective of this study was to provide a systematic review of the interventions developed to enhance adherence to oral therapies in patients with BC. The aim was to offer a detailed and accessible resource for both researchers and HCPs, presenting a current and comprehensive overview of existing strategies in this area. A further goal of the study was to examine in depth the specific content (the 'active components') of these interventions, with a particular focus on identifying the BCTs they incorporate. Although the effectiveness of the interventions was not directly compared, the content analysis allowed for the formulation of preliminary considerations regarding which techniques might prove more promising in supporting medication adherence. To achieve these aims, it was crucial to adopt the shared, consensus-based, and reliable framework provided by the BCTT (Michie et al., 2013).

3.1.2 Material and methods

Search strategy

To identify all relevant studies reporting interventions aimed at improving adherence to oral therapies in BC patients, a search string was developed by combining keywords related to four key domains: adherence, oral antineoplastic treatment, BC, and intervention (the complete search string is available in Appendix 1). The literature search was conducted across four electronic databases, PubMed, Scopus, Embase, and Ovid (Journals@Ovid), for records published up to 17 October 2022. Additionally, the reference lists of pertinent articles were manually screened to identify further eligible studies. The review was conducted in accordance with the PRISMA guidelines (Page et al., 2021), ensuring that it was reported in a transparent, reproducible, and standardised manner. It was registered in the international prospective register of systematic reviews (PROSPERO; registration number: CRD42022298552).

Inclusion and exclusion criteria

To be considered eligible for inclusion, studies had to meet the following criteria: (1) they reported the design, evaluation, or implementation of an intervention aimed at improving adherence to oral anticancer therapies; (2) they included, or intended to include (in the case of study protocols), at least a subgroup of patients with BC, with results specifically reported for this population; (3) they were available in English; and (4) full-text access was available online. Conference papers, editorials, and commentaries were excluded due to the lack of detailed information on the intervention content.

Screening and quality assessment

Two reviewers independently screened titles and abstracts to assess eligibility, classifying records as "accepted," "rejected," or "for discussion." Any discrepancies were referred to a third reviewer and resolved through discussion until consensus was reached. Full-texts of the included studies were subsequently examined by one reviewer to confirm their relevance and compliance with the eligibility criteria. When full-texts were not freely accessible online, the corresponding authors were contacted to request them.

The methodological quality of the included studies was assessed using the Downs and Black's methodological quality scale (Downs & Black, 1998), a 27-item tool evaluating five domains of methodological quality: reporting bias (RB), external validity (EV), internal validity (IV), confounding (selection bias, SB), and statistical power (P). Two reviewers independently conducted the quality appraisal, with any disagreements resolved through discussion until consensus was reached.

In line with previous systematic reviews (Hooper et al., 2008; Silverman et al., 2012), the assessment of statistical power was simplified: one point was awarded if the sample size calculation had been reported and justified, and zero if it was not reported or insufficient to ensure adequate statistical power.

Data extraction and summary

From each included study, the following information was extracted: authors, year of publication, country, patient sample, cancer stage, type of oral therapy, study design, mode of delivery, adherence measurement methods, a brief description of the intervention, and, where applicable, the comparison or control condition, timing of assessment(s), and main findings. Data extraction was performed by one author and verified by a second. A synthesis of the extracted data is presented in Tables 1 and 2.

In addition, the content of each intervention was analysed using the BCTT (Michie et al., 2013). Following completion of the official BCTT online training (www.bct-taxonomy.com), the interventions were coded by identifying and categorising the BCTs employed in each study. Each intervention was broken down into its distinct components to highlight the techniques used to support medication adherence. The BCTs identified across the included studies are summarised in Table 3.

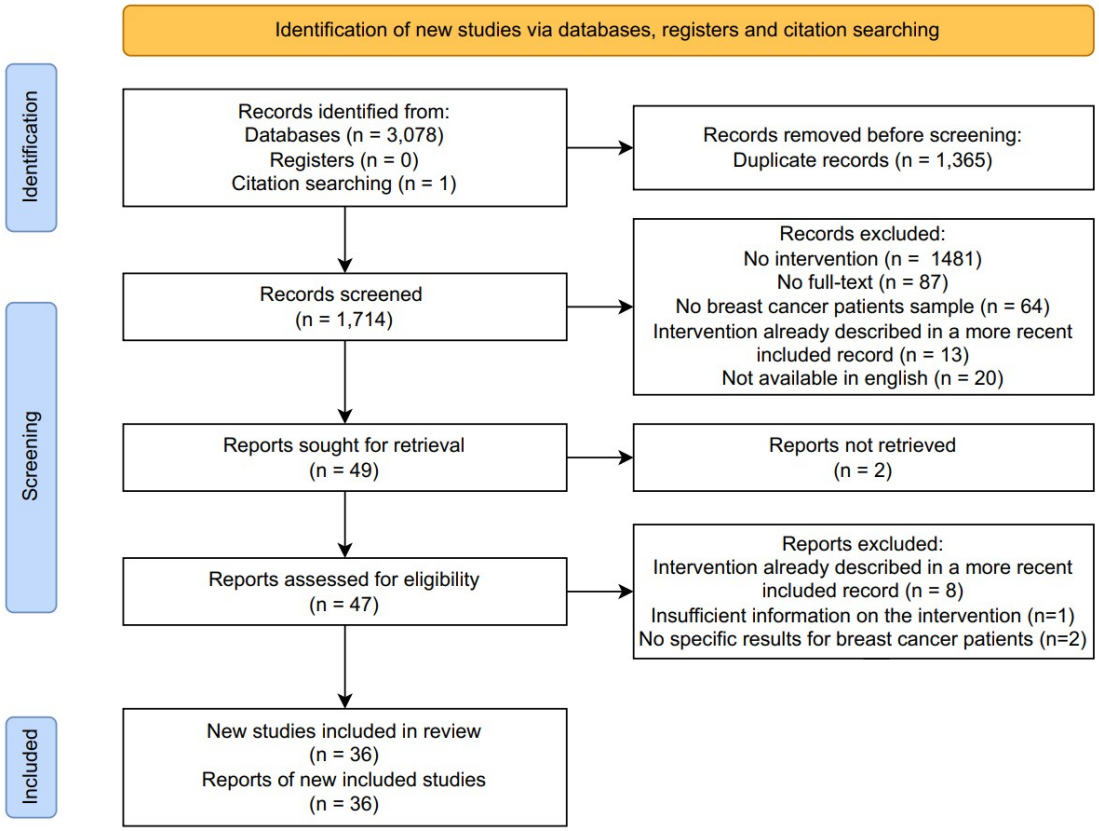
3.1.3 Results

Summary of study characteristics

The initial search identified 3,079 records. Following the removal of duplicates and the screening of titles and abstracts, 49 articles were deemed potentially eligible. Among these, two were excluded due to the unavailability of the full text, while an additional

11 were excluded after full-text assessment. A detailed description of the selection process is provided in Figure 1.

Figure 1. *PRISMA flow diagram of the study selection process for Study 1.*



Adapted from Pezzolato et al., Psycho-Oncology, 2023.

The studies included in the review were published between 2009 and 2022. The majority were conducted in North America (19 studies) (Arch et al., 2022; Bhandari et al., 2019; Bluethmann et al., 2021; Chalela et al., 2018; Ell et al., 2009; Graetz et al., 2018; Hershman et al., 2020; Jacobs et al., 2022; Krok-Schoen et al., 2019; Lee et al., 2020; Meguerditchian et al., 2016; Mougalian et al., 2017; Myers et al., 2022; Paladino et al., 2019; Ream et al., 2021; Sanft et al., 2021; Shelby et al., 2019; Wagner et al., 2016; Yanez et al., 2022), followed by Europe (10 studies) (Ferraris et al., 2020; Hadji et al., 2013; Heisig et al., 2015; Jacob et al., 2015; Mamguem Kamga et al., 2020; Moon et al., 2019; Riis et al., 2020; Smith et al., 2022; von Blanckenburg et al., 2013; Ziller et al., 2013). One study was international, involving data collection across 18 countries (Markopoulos et al., 2015), another was carried out in Africa

(Getachew et al., 2022), and five studies took place in Asia (Komatsu et al., 2020; H. R. Park et al., 2022; Tan et al., 2020; J. Yu et al., 2021; K.-D. Yu et al., 2012).

With regard to study design, 24 of the included studies were randomised controlled trials, nine of which were study protocols and four were pilot studies. The remaining 12 studies comprised retrospective and prospective cohort studies, single-arm studies, and non-randomised controlled studies; among these, six were pilot studies and one was a study protocol.

The 36 studies relied on a range of diverse adherence measures: 10 studies assessed adherence exclusively through prescription data, pill counts, or electronic medication monitors. The other studies used a variety of approaches: in 26 papers, adherence was measured using self-report questionnaires, either alone (n = 13) or combined with other methods, including prescription data, HCP reports, or urine assays. The use of multiple adherence measures can be regarded as a good practice. Since, as discussed in the Chapter 1 of this thesis, each method carries its own strengths and limitations, their combination allows for a more robust and reliable assessment of participants' adherence.

The vast majority of the studies reviewed focused exclusively on adherence to oral endocrine therapies, such as tamoxifen or aromatase inhibitors. In contrast, only one study specifically investigated adherence to oral chemotherapy (i.e., capecitabine and tegafur/gimeracil/oteracil) and targeted therapy (i.e., lapatinib), without including endocrine treatments (Komatsu et al., 2020).

More than one third of the included studies (n = 14) explicitly grounded their interventions in theoretical frameworks or models. Among these, Social Cognitive Theory (Bandura, 1998) emerged as the most frequently used (Bluethmann et al., 2021; Chalela et al., 2018; Paladino et al., 2019; Sanft et al., 2021; Shelby et al., 2019), followed by Cognitive Behavioural Therapy (Antoni, 2003; Jacobs et al., 2022; Mann et al., 2012; Ream et al., 2021; Safren et al., 2007; von Blanckenburg et al., 2013). Other studies drew on a range of theoretical approaches, including models of concordance and shared decision-making (Jordan et al., 2002; Komatsu et al., 2020), the TPB (Ajzen, 1991; Moon et al., 2019), the HBM (Ell et al., 2009; Jones et al., 2014; Yanez et al., 2022), the CSM (Leventhal et al., 2016; Moon et al., 2019), Acceptance and Commitment Therapy (Arch et al., 2022; Hayes et al., 2006; Smith et al., 2022), Mindfulness-Based Stress Reduction (Kabat-Zinn et al., 1985; Yanez et al., 2022), and Self-Affirmation Theory (Arch et al., 2022; Steele, 1988). A description of some of these theoretical models can be found in Chapter 2 of this thesis.

The sample sizes in the included studies ranged from 27 to 7,867 participants, with a cumulative total of 28,528 patients with BC. Only one study focused exclusively on patients with mBC (Komatsu et al., 2020), while three others enrolled mixed samples

comprising both early-stage and metastatic patients (Getachew et al., 2022; Heisig et al., 2015; Ziller et al., 2013). In two studies, the cancer stage of participants was not specified (Chalela et al., 2018; Jacob et al., 2015), whereas all remaining studies included only patients diagnosed with early-stage BC.
A summary of the key characteristics of the included studies is presented in Table 1.

Type of intervention
The interventions described across the included studies varied considerably in both format and content. They were delivered through different modalities, including face-to-face sessions, electronic devices (i.e., computers, tablets, telephones, or smartphones), written materials, or a combination of these approaches. The following sections summarise the modes of delivery adopted, while the specific intervention contents are detailed in the paragraph dedicated to BCTs.
A more detailed description of each intervention is provided in Table 2.

Table 1. *Characteristics of the studies included in Study 1.*

First author, year	Country	Patient sample, cancer stage	Study design	Mode of delivery	Method(s) of adherence
Arch, 2022	USA	88, early-stage I: 43 C: 45	RCT†	eHealth (online self-paced intervention)	Self-report and EMM
Bhandari, 2019	USA	86, early-stage	Single-arm study†	Other	Pill count
Bluethmann, 2021	USA	N.a., early-stage	RCT‡	eHealth (videoconference)	Self-report and MPR
Chalela, 2018	USA	N.a.	RCT‡	eHealth (mobile app)	Self-report and medical records
Ell, 2009	USA	237, early-stage I: 123 C: 114	RCT	eHealth (written/telephone)	Pharmacy records
Ferraris, 2020	Italy	88, early-stage I: 44 C: 44	RCT	Other	Self-report
Getachew, 2022	Ethiopia	162, all stages I: 87 C: 75	RCT	In person (with also eHealth elements and written materials)	Self-report and MPR
Graetz, 2018	USA	48, early-stage I: 23 C: 25	RCT†	eHealth (mobile app)	Self-report
Hadji, 2013	Germany	4844, early-stage I: 2442 C: 2402	RCT	Educational/written material	Self-report and prescription data
Heisig, 2015	Germany	174, all stages	Single-arm study	Educational/written material	Self-report
Hershman, 2020	USA	724, early-stage I: 360 C: 364	RCT	eHealth (text messaging)	Self-report and urine assays
Jacob, 2015	Germany	4915, N.a. I: 1874 C: 3041	Retrospective cohort study	Other	Electronic medical records
Jacobs, 2022	USA	100, early-stage I: 50 C: 50	RCT†	eHealth (videoconference)	Self-report and EMM
Komatsu, 2020	Japan	155, metastatic I: 78 C: 77	RCT	In person	MPR
Krok-Schoen, 2019	USA	39, early-stage	Single-arm study†	eHealth (mobile app)	Self-report

First author, year	Country	Patient sample, cancer stage	Study design	Mode of delivery	Method(s) of adherence
Lee, 2020	USA	7867, early-stage I: 4287 C: 3580	Retrospective cohort study	Educational/written material	MPR
Mamguem Kamga, 2020	France	N.a., early-stage	RCT‡	eHealth (tablet)	Self-report
Markopoulos, 2015	International (18 countries)	2757, early-stage I: 1379 C: 1378	RCT	Educational/written material	Self-report and provider report
Meguerditchian, 2016	Canada	N.a., early-stage	Non-randomized controlled study‡	eHealth (eHealth tool for providers)	MPR
Moon, 2019	UK	41, early-stage	Single-arm study†	Educational/written material	Self-report
Mougalian, 2017	USA	200, early-stage I: 100 C: 100	Non-randomized controlled study†	eHealth (mobile app)	Self-report
Myers, 2022	Canada	27, early-stage	Single-arm study†	eHealth (videoconference)	Self-report
Paladino, 2019	USA	N.a., early-stage	RCT‡	eHealth (mobile app)	Self-report and EMM
Park, 2021	South Korea	61, early-stage I: 31 C: 30	RCT	eHealth (mobile app)	EMM
Ream, 2021	USA	135, early-stage I1: 44 I2: 49 C: 42	RCT	In person	Self-report
Riis, 2020	Denmark	134, early-stage I: 65 C: 69	RCT†	Other	Electronic medical records
Sanft, 2021	USA	N.a., early-stage	RCT‡	In person	Self-report and urine assays
Shelby, 2019	USA	N.a., early-stage	RCT‡	eHealth (telephone)	Self-report and EMM
Smith, 2022	UK	N.a., early-stage	RCT‡	eHealth (videoconference)	Self-report
Tan, 2020	Singapore	244, early-stage I: 123 C: 121	RCT	eHealth (text messaging)	Self-report
Von Blanckenburg, 2013	Germany	N.a., early-stage	RCT‡	In person	Self-report
Wagner, 2016	USA	230, early-stage I: 36 C1: 163 C2: 31	Cohort study†	eHealth (telephone)	MPR

First author, year	Country	Patient sample, cancer stage	Study design	Mode of delivery	Method(s) of adherence
Yanez, 2022	USA	N.a.	RCT‡	eHealth (online tool)	Self-report, EMM and medical/pharmaceuticals records
Yu, 2012	China	516, early-stage I: 252 C: 264	Non-randomized controlled study	Educational/written material	MPR
Yu, 2021	China	4475, early-stage I: 648 C1: 2966 C2: 861	Retrospective cohort study	eHealth (mobile app)	Self-report
Ziller, 2013	Germany	181, all stages I1: 57 I2: 57 C: 57	RCT	eHealth (written/telephone)	Self-report and MPR

† = pilot study; ‡ = study protocol; RCT = randomized controlled trial; I: intervention group; C = control group; MPR = medication possession ratio; EMM = electronic medication monitor; n.a. = not available.

Table 2. *Characteristics of the interventions included in Study 1.*

First author, year	Intervention(s)	Control or comparison group(s)	Time of assessment(s)	Results
Arch, 2022	Values intervention + adjuvant endocrine therapy education (REACH - Resources and Education for Adherence to Cancer Hormonal therapy)	Adjuvant endocrine therapy education	Baseline, 1 week, 3 and 6 months (self-report) and each month for 6 months (EMM)	Significantly higher adherence in intervention group (adherence rate: 87.8 vs. 96.3%, p = 0.027), but only in the first month
Bhandari, 2019	Daily blister pack (bubble packaging)	N.a.	1 year	Adherence was higher than that in historical studies (adherence rate: 97%)
Bluethmann, 2021	An evidence-based physical activity program that includes bi-weekly, supervised exercise sessions plus 30 min of education. It included: 8 weeks of supervised sessions plus 8 weeks of self-guided home sessions with periodic phone coaching	Enhanced standard care (written materials and assessment visits)	Baseline, 4, 6 and 12 months	N.a.
Chalela, 2018	App + patient navigation	Standard care	Baseline, 3 and 6 months	N.a.
Ell, 2009	Written information + patient navigation	Enhanced standard care (written materials)	6 and 12 months	No significant differences in adherence between the groups; d = 0.132
Ferraris, 2020	One oral tablet/day containing 80 mg of red clover extract for 24 months + diet-lifestyle intervention	Placebo + diet-lifestyle intervention	24 months	The adherence of the total sample was higher than reported in literature (proportion of adherent patients: 89%)
Getachew, 2022	A nurse-delivered comprehensive package of services including education, provision of written material, reminder with phone call, additional empathetic counselling and monitoring of medication refill	Standard care	Baseline, 6 and 12 months	Participants in the intervention group reported significantly higher adherence at 12 months (proportion of adherent patients: 70 vs 44.8%, p = 0.036); d = 0.580
Graetz, 2018	App + reminder (weekly reminders to use the app)	App (no reminders)	Baseline and 6-8 weeks	Participants in the app + reminder group reported significantly higher adherence (proportion of adherent patients:100 vs. 72.7%, p < 0.05); d = 1.684
Hadji, 2013	Standard care + educational materials	Standard care	Baseline, 12 and 24 months	No significant differences in adherence between the groups; d = 0.016
Heisig, 2015	Enhanced information	N.a.	Baseline and 3 months	Post-intervention adherence was higher, but the difference wasn't statistically significant; d = 0.169
Hershman, 2020	Text messaging (twice a week over 36 months)	No text messaging	Baseline and every 3 months up to 36 months	No significant differences in adherence between the groups; d = 0.229
Jacob, 2015	Disease management program	Standard care	3 years	The rate of therapy discontinuation at 3 years was lower in DMP patients (32.7 vs. 39.6%, p < 0.001); d = 0.166

First author, year	Intervention(s)	Control or comparison group(s)	Time of assessment(s)	Results
Jacobs, 2022	A patient-centred, evidence-based, small-group, videoconference intervention (Symptom-Targeted Randomised Intervention for Distress and Adherence to Adjuvant Endocrine Therapy – STRIDE)	Medication monitoring control group	Baseline, 12 and 24 weeks	No significant differences in adherence between the groups; $d = 0.07$
Komatsu, 2020	Nurse-led self-management intervention	Standard care	Baseline and 3 months	No significant differences in adherence between the groups; $d = 0.048$
Krok-Schoen, 2019	A smartphone, text-based reminder system to increase adherence, coupled with an interactive smartphone app	N.a.	Baseline and 3 months	Significant improvements in adherence rate ($p = 0.015$); $d = 0.493$
Lee, 2020	Health system outreach program	Pre-outreach cohort	Every 12 months after prescription	Adherence (+4.9%; $d = 0.125$) and discontinuation rates (-4%) improved modestly
Mamguem Kamga, 2020	Systematic HRQoL assessment (using a tablet, prior to each consultation, with presentation of scores to clinicians) coupled with therapeutic information	Standard care	Baseline and 12 months	N.a.
Markopoulos, 2015	Educational materials	Standard care	Baseline, 1 and 2 years	Compliance did not improve; $d = 0.004$
Meguerditchian, 2016	A patient-specific, real-time eHealth alert delivered at point-of-care	Standard care	Baseline and 18 months	N.a.
Moon, 2019	A self-management intervention via a paper booklet	N.a.	Baseline and completion of the intervention (2-12 weeks)	Unintentional non-adherence was lower after the intervention, but the difference wasn't statistically significant; $d = 0.15$
Mougalian, 2017	A bidirectional text-message application that tracks adherence, records symptoms, and alerts the clinical team	Historical control	Every week for 3 months	Intervention group reported high adherence (proportion of adherent patients: 93.3%)
Myers, 2022	A virtual supervised strength and aerobic exercise program (BE-FIT—Breast Cancer Endocrine Therapy Fitness)	N.a.	Baseline and 6 weeks	Post-intervention adherence was higher, but the difference wasn't statistically significant; $d = 0.333$
Paladino, 2019	1: app and weekly reminders to use it; 2: app, weekly reminders and feedback on the use of the app	Standard care	12 months (EMM) and 12, 18, 24, 30, 36 months (self-report) when possible	N.a.
Park, 2021	A smart pill bottle paired with the Pillsy mobile application	Standard care	28 days	Significantly higher adherence rate in intervention group (97.3 vs. 88.33%, $p = 0.004$); $d = 0.787$
Ream, 2021	1: a CBT intervention comprising cognitive behavioural components of CBSM; 2: a relaxation training modelled after the relaxation component of CBSM	Health education	Baseline, post-intervention (5 weeks), 6 and 12 months and 8 years	Significantly higher adherence in intervention group 2
Riis, 2020	Individualized follow-up care	Standard follow-up care	Baseline and every 3 months for 2 years	No significant differences in adherence between the groups; $d = 0.301$

First author, year	Intervention(s)	Control or comparison group(s)	Time of assessment(s)	Results
Sanft, 2021	A yearlong, 16 session, nutrition and exercise intervention	Standard care	Baseline, post-chemotherapy, 1 and 2 years	N.a.
Shelby, 2019	A telephone-based coping skills training that teaches patients adherence skills and techniques for coping with problematic symptoms	Health education	Baseline, 3, 6, 12, and 18 months	N.a.
Smith, 2022	An ACT intervention including an individual session and three group sessions + access to a website containing evidence-based methods for self-managing side-effects	Standard care	Baseline, 3 and 6 months	N.a.
Tan, 2020	Text-messaging reminder	Standard care	Self-report: baseline, 6 months and 1 year; hormone level: baseline and 1 year	Significantly higher adherence in intervention group (proportion of adherent patients: 72.4 vs. 59.5%, $p = 0.034$) at 6 months; $d = 0.318$
Von Blanckenburg, 2013	Side-effect prevention training	Control group: standard care; Attention control group: supportive therapy	Baseline, post-treatment, 3 and 6 months	N.a.
Wagner, 2016	Outreach conducted by health plan care managers	1 (adherent group): standard care; 2 (not contacted): standard care	Baseline and 6 months	Adherence in the intervention group was higher, but the difference wasn't statistically significant; $d = 0.557$
Yanez, 2022	An online, mindfulness-based program (MyJourney) designed to improve adherence to endocrine therapy	Health education website	Baseline, 4 and 8 weeks, 6 and 12 months	N.a.
Yu, 2012	A patient support program comprising educational support material and a follow-up reminder service	Standard care	1 year	No significant differences in persistence between the groups; $d = 0.016$
Yu, 2021	An app enabling communication between patients and medical workers and providing personalized management	1 (pre-app): standard care; 2 (app non-used): standard care	Every 3 months within the first 2 years after surgery, every 6 months between 3 and 5 years, and once a year after 5 years	The use of the app was not significantly associated with treatment compliance; $d = 0.331$
Ziller, 2013	1: reminder letters and information booklet; 2: telephone reminder and information	Standard care	12 months	Adherence in the intervention groups was higher, but the difference wasn't statistically significant (1: $d = 0.311$; 2: $d = 0.274$)

ACT = acceptance and commitment therapy; CBSM = cognitive behavioural stress management programme; CBT = cognitive behavioural therapy; d = Cohen's d; DMP = disease management program; EMM = electronic medication monitor; HRQoL = health-related quality of life; n.a. = not available.

eHealth interventions

Most of the interventions (*n* = 21) were delivered through electronic means, including computers, tablets, telephones, or smartphones, with several of these (*n* = 7) specifically employing mobile applications. Among the eHealth interventions examined, five studies reported significant improvements in medication adherence (Arch et al., 2022; Graetz et al., 2018; Krok-Schoen et al., 2019; H. R. Park et al., 2022; Tan et al., 2020). These effective interventions largely relied on the use of dedicated mobile applications featuring adherence monitoring tools and reminder systems, with two exceptions: one study tested a text message reminder system (Tan et al., 2020), while another delivered a brief values-based intervention online, supplemented by educational materials (Arch et al., 2022). The remaining 16 eHealth interventions adopted various delivery modes, such as telephone-based patient navigation, outreach initiatives, or the provision of information and reminders (Ell et al., 2009; Wagner et al., 2016; Ziller et al., 2013); mobile applications designed to enhance communication between patients and HCPs (J. Yu et al., 2021); videoconferencing for individual or group-based interventions (Jacobs et al., 2022; Myers et al., 2022); and text messaging aimed at symptoms monitoring, adherence tracking, or education (Hershman et al., 2020; Mougalian et al., 2017). None of these studies, however, demonstrated significant effects on adherence outcomes. Additionally, eight of the included studies were protocols (Bluethmann et al., 2021; Chalela et al., 2018; Mamguem Kamga et al., 2020; Meguerditchian et al., 2016; Paladino et al., 2019; Shelby et al., 2019; Smith et al., 2022; Yanez et al., 2022) outlining the development and planned evaluation of eHealth strategies aimed at improving adherence to oral anticancer therapies.

In-person interventions

In five of the studies reviewed, the interventions were delivered face-to-face by HCPs such as nurses, clinical psychologists, dietitians, or psychology students (Getachew et al., 2022; Komatsu et al., 2020; Ream et al., 2021; Sanft et al., 2021; von Blanckenburg et al., 2013). Among these, two randomised controlled trials reported significant improvements in adherence (Getachew et al., 2022; Ream et al., 2021). In the study by Ream and colleagues' (Ream et al., 2021), three interventions were compared: a Cognitive Behavioural Stress Management programme including multiple components, a relaxation training based on the relaxation elements of the same programme, and a health education programme. In the second study, a comprehensive, nurse-led intervention designed to enhance adherence to tamoxifen was tested against standard care and yielded positive results (Getachew et al., 2022). Other interventions delivered in person included a nurse-led self-management

programme, training focused on preventing side effects, and a nutrition and exercise intervention aimed at reducing treatment-related adverse effects (Sanft et al., 2021; von Blanckenburg et al., 2013; Ziller et al., 2013).

Interventions delivered through written material

In six of the studies included in this review, the central component of the interventions consisted in the provision of various forms of written material, such as letters, self-management booklets, or informational leaflets. In one of these studies, Lee et al. (Lee et al., 2020) evaluated the effectiveness of an outreach programme based on mailed reminder letters, with optional telephone follow-up, which resulted in a significant improvement in adherence.

Other interventions involved the distribution of written educational materials focusing on the mechanisms of action, benefits, and potential side effects of oral anticancer therapies, provided either as stand-alone resources (Hadji et al., 2013; Heisig et al., 2015; Markopoulos et al., 2015) or supplemented by a telephone follow-up reminder service (K.-D. Yu et al., 2012). One study, in particular, tested a psychoeducational self-management booklet combining medication and side-effect information with cognitive-behavioural therapy techniques, such as goal setting and problem solving (Moon et al., 2019).

Other interventions

The remaining interventions did not fit neatly into any of the previously described categories. One study sought to improve adherence by dispensing medications in daily blister packs to facilitate correct intake (Bhandari et al., 2019). Another investigation explored whether dietary supplements combined with lifestyle modifications could help reduce treatment-related side effects and, in turn, enhance adherence (Ferraris et al., 2020). Additionally, two studies tested individualised approaches: one tailored follow-up care based on electronic patient-reported outcomes (Riis et al., 2020), while the other assessed the impact of a disease management programme, a patient-centred, multidisciplinary approach designed to enhance the overall quality of care, on adherence levels (Jacob et al., 2015).

Behaviour change techniques

The interventions were analysed and their content categorised using the BCTT (Michie et al., 2013). This process led to the identification of 25 distinct techniques out of the 93 included in the taxonomy. The number of techniques applied within each intervention varied considerably, ranging from none, where the intervention influenced adherence only indirectly, making it impossible to classify using this framework, to a

maximum of 17 techniques. A detailed summary of the BCTs used across interventions is presented in Appendix 2.

The techniques most frequently identified were: "problem solving" (*n* = 14), "social support" (*n* = 20), "information about health consequences" (*n* = 22), and "prompts/cues" (*n* = 16). Among the interventions associated with statistically significant improvements in adherence, the most commonly applied techniques were "feedback on behaviour" (*n* = 4), "information about health consequences" (*n* = 4) and "prompts/cues" (*n* = 6). For a full account of these techniques, readers are referred to the original taxonomy proposed by Michie and colleagues (Michie et al., 2013).

Risk of bias

The methodological quality of the studies was assessed using the Downs and Black's scale (Downs & Black, 1998). A summary of the quality assessment is presented in Table 3, where lower scores indicate a higher risk of bias. Due to the inherent differences in the information available between study protocols and studies reporting actual results, their scores have been presented separately within the table.

Focusing on the studies that reported the implementation and outcomes of an intervention (*n* = 26), selection bias emerged as the area with the highest risk, with an average score of 3.58 (SD = 2.14, range = 0–6). Internal validity and external validity received intermediate scores, with means of 4.73 (SD = 0.96, range = 0–7) and 2.08 (SD = 0.39, range = 0–3), respectively. The reporting bias dimension showed the lowest risk, with a mean score of 8.81 (SD = 0.69, range = 0–11). Notably, only 10 out of these 26 studies scored one point on the statistical power dimension, indicating that the majority failed to adequately address sample size calculation or power consideration.

Study protocols, as expected, obtained lower overall quality scores compared to completed studies (mean total score: 15.2 against 19.58). Similarly, the individual dimension scores were consistently lower for protocols: RB = 6.5 (SD = 0.71), EV = 1.2 (SD = 0.63), IV = 3.1 (SD = 0.32), and SB = 3.5 (SD = 1.27). Interestingly, statistical power was the only area where protocols performed better: with the exception of one protocol, all the others included a power analysis or sample size estimation.

Table 3. *Risk of bias assessment – Downs & Black's methodological quality scale.*

First author, year	RB (0-11)	EV (0-3)	IV (0-7)	SB (0-6)	P (0-1)	Tot (0-28)
Arch, 2022	9	3	6	6	1	25
Bhandari, 2019	8	2	4	0	0	14
Ell, 2009	7	2	6	5	0	20
Ferraris, 2020	10	1	7	5	1	24
Getachew, 2022	9	2	4	1	1	17
Graetz, 2018	8	2	5	4	0	19
Hadji, 2013	9	2	4	6	1	22
Heisig, 2015	9	2	4	1	0	16
Hershman, 2020	9	2	5	6	1	23
Jacob, 2015	7	3	3	2	0	15
Jacobs, 2022	9	2	5	6	1	23
Komatsu, 2020	9	2	5	6	0	22
Krok-Schoen, 2019	9	2	3	0	0	14
Lee, 2020	9	3	5	3	0	20
Markopoulos, 2015	8	2	4	6	1	21
Moon, 2019	9	2	4	1	0	16
Mougalian, 2017	9	2	5	2	0	18
Myers, 2022	10	2	5	1	0	18
Park, 2021	9	2	5	5	0	21
Ream, 2021	9	2	5	4	0	20
Riis, 2020	9	2	5	5	0	21
Tan, 2020	9	2	5	6	0	22
Wagner, 2016	9	2	5	3	0	19
Yu, 2012	9	2	5	2	1	19
Yu, 2021	9	2	3	2	1	17
Ziller, 2013	9	2	6	5	1	23
Means	8.81	2.08	4.73	3.58	0.38	19.58
SD	0.69	0.39	0.96	2.14	0.50	3.07
Protocols						
Bluethmann, 2021	6	1	3	4	1	15
Chalela, 2018	6	1	3	4	1	15
Mamguem Kamga, 2020	7	1	3	3	1	15
Meguerditchian, 2016	7	0	3	0	1	11
Paladino, 2019	8	2	3	4	1	18
Sanft, 2021	6	1	3	4	1	15
Shelby, 2019	6	2	3	4	0	15
Smith, 2022	7	2	3	4	1	17
Von Blanckenburg, 2013	6	1	4	4	1	16
Yanez, 2022	6	1	3	4	1	15
Means	6.5	1.2	3.1	3.5	0.9	15.2
SD	0.71	0.63	0.32	1.27	0.32	1.81

RB = reporting bias; EV = external validity; IV = internal validity; SB = selection bias; P = power; SD = standard deviation.

3.1.4 Discussion

The growing prevalence of oral anticancer therapies, combined with the well-documented negative impact of medication non-adherence, underpins the increasing

attention devoted to the development of adherence-promoting interventions for patients with BC patients. This rising interest is reflected in the steady growth of research in this area: notably, 25 out of the 36 studies included in this review were published between 2018 and 2022.

Nearly all the studies included in this review focused on adherence to oral endocrine therapies (such as tamoxifen and aromatase inhibitors), with the sole exception of one study that addressed adherence to oral chemotherapy (i.e., capecitabine and tegafur/gimeracil/oteracil) and targeted therapy (i.e., lapatinib) (Komatsu et al., 2020). The predominance of research on endocrine therapy confirms the trend already noted in Chapter 1 and may reflect the longer duration of these treatments, which are typically prescribed for five to ten years, compared to the usually shorter courses of oral chemotherapy and targeted treatments (Waks & Winer, 2019). Prolonged treatment durations are known to increase the likelihood of adherence challenges, as non-adherence often rises over time following treatment initiation (Yussof et al., 2022). Moreover, the more limited attention paid to adherence in the context of oral chemotherapy and targeted therapies appears consistent with the findings of the study by Komatsu and colleagues (Komatsu et al., 2020), who conducted a randomised controlled trial to evaluate the impact of a self-management support programme on adherence among patients with mBC receiving oral chemotherapy or targeted therapy. The intervention did not yield significant improvements in adherence, as both the intervention and control groups reported high adherence rates, with a medication possession ratio exceeding 90%. Notably, another important characteristic of this study is its focus on mBC. Metastatic disease differs substantially from early stages not only in clinical terms, but also in how patients perceive and relate to their treatment. These differences in treatment representations are explored in detail in Chapter 4, particularly in Study 5, where the NCF is applied to gain deeper insight into how individuals living with mBC view their therapy. Within the context of this systematic review, the inclusion of this study offered a broader perspective on adherence across various classes of oral anticancer therapies and disease stages. It also helped to highlight the disproportionate emphasis in the literature on endocrine treatments and early-stage BC, underscoring the need for future research in less explored areas. In line with this gap, Study 4 and 5 of this thesis aim to advance the understanding of non-adherence in the mBC population: first, by giving voice to patients' own experiences and perspectives, and then by conducting a pilot study of a multi-component intervention while collecting data on adherence and relevant psychological variables. A full account of these studies is presented in Chapter 4.

The studies included in this review adopted a range of strategies aimed at improving medication adherence, underscoring the notable heterogeneity that characterises this

area of research. Despite the diversity of approaches, a clear predominance of eHealth interventions emerged from the findings. Indeed, in most of the reviewed studies (21 out of 36), interventions were delivered primarily via the Internet and/or communication technologies, reflecting the growing importance and integration of digital health solutions within cancer care (Kondylakis et al., 2013; Penedo et al., 2020). This trend, together with the increasing use of AI in healthcare, motivated the rationale for Study 3, which specifically examined the contribution of AI in supporting adherence among BC patients. While AI, mainly in the form of ML, was frequently employed in predictive modelling studies, its use to enhance eHealth interventions was limited, with only a single study describing an AI-powered chatbot. These observations are further discussed in Study 3, providing a more detailed account of AI's potential and current limitations in this domain.

The studies reviewed displayed considerable diversity, not only in the specific features of the interventions but also in how adherence was measured, the length of follow-up periods, and the types of study designs employed. A significant portion of the selected papers consisted of study protocols (n = 10), which, although not providing data on intervention efficacy, were included to broaden and update the overall picture of existing strategies aimed at improving adherence. The pronounced variability across these studies limits the possibility of directly comparing their outcomes; for this reason, assessing and ranking intervention effectiveness was beyond the scope of this review. Nonetheless, by examining in depth the characteristics and content of the interventions, some tentative considerations can be drawn, offering a starting point for generating hypotheses to be tested in future investigations. The following section presents and discusses some of these hypotheses.

To begin with, the range of contents and outcomes observed across interventions reinforces the conceptualisation of non-adherence as a complex, multifaceted issue, unlikely to be addressed effectively through one-size-fits-all solutions (Yussof et al., 2022). Among the 26 studies that provided results, only nine reported statistically significant improvements in adherence. A comparable finding was noted in a previous review, which attributed the limited effects observed to the brevity of follow-up periods: since adherence tends to decline over time, short-term assessments may fail to fully capture the interventions' long-term impact (Hurtado-de-Mendoza et al., 2016). It has also been suggested that participants' awareness of being monitored for adherence might itself prompt greater compliance with prescribed regimens. While these factors offer partial explanations, they do not entirely account for the overall modest impact of many interventions, underscoring the ongoing need for more effective strategies tailored to the specific challenges faced by this clinical population (Finitsis et al., 2019; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). In this

context, identifying the most promising BCTs becomes a crucial step. The use of the BCTT enabled a more structured and detailed analysis of intervention components. The insights discussed below are drawn specifically from the subset of 26 studies that reported outcome data, excluding the protocols.

Interestingly, the BCT "feedback on behaviour", which involves monitoring a targeted behaviour and providing corresponding feedback, was present in four out of the nine interventions that reported significant improvements in adherence, while it appeared in only one of the 18 studies with non-significant outcomes. This distribution may point to the potential effectiveness of this specific technique in promoting medication adherence (Humphreys et al., 2021; Schembre et al., 2018).

Although the BCT "information about health consequences" appeared just as frequently among the interventions that significantly improved adherence (n = 4), its broader distribution across studies with non-significant results (identified in 11 out of 18) suggests that this technique alone may have limited impact. In the context of the included interventions, this technique involved informing patients about the potential outcomes of adherence or non-adherence to their prescribed oral treatments. While such information may support patients in making informed decisions, it does not appear to be sufficient, on its own, to induce a meaningful change in adherence behaviours. This aligns with previous findings in the literature which have questioned the efficacy of educational strategies when used alone (Hurtado-de-Mendoza et al., 2016; McGrady et al., 2023). The results presented here offer further support to this perspective, reinforcing the idea that non-adherence is a multifaceted issue, shaped by the interplay of diverse psychological, social, and contextual factors, rather than a mere lack of knowledge (McGrady et al., 2023; Moon et al., 2017; Yussof et al., 2022).

Another BCT that appears particularly promising is the use of "prompts/cues." This strategy was included in six out of the nine interventions that achieved significant improvements in adherence, compared to only seven out of the 18 that did not. Typically, this technique involves the use of reminder systems, delivered at varying intervals (e.g., daily, weekly, or monthly), and often integrated into specifically designed mobile applications. The implementation of prompts or cues may be especially effective in addressing unintentional non-adherence, which happens when patients fail to follow prescribed regimens due to forgetfulness or misunderstanding, rather than through a deliberate decision to deviate from treatment (Atkins & Fallowfield, 2006). In this sense, supporting medication-taking behaviour through external reminders may serve as a simple yet effective tool for mitigating one of the most common barriers to consistent adherence (Skrabal Ross et al., 2020).

The three BCTs discussed thus far, namely, "feedback on behaviour," "information about health consequences," and "prompts/cues," were incorporated into the

intervention developed for mBC patients in Study 5, with the aim of pilot testing their feasibility and perceived usefulness. As detailed in Chapter 4, the intervention was feasible, low-cost and well received by participants. However, the high adherence rates observed made in the sample prevented even preliminary conclusions from being drawn regarding the effectiveness of these three BCTs. Further testing in larger and less adherent populations will therefore be required to establish their potential impact.

To conclude this overview of the most frequently employed BCTs, the technique of "social support" will be briefly addressed. Although it has been identified as a relevant factor influencing adherence to endocrine therapy in BC patients, as highlighted by a recent review (Yussof et al., 2022), the inclusion of the BCT "social support" in the interventions examined did not consistently lead to significant improvements. In fact, among the studies reporting intervention outcomes, this technique was associated with statistically significant increases in adherence in only three out of 15 cases in which it was employed. The modest impact of social support interventions may once again reflect the multifaceted nature of adherence, which is often influenced by a dynamic interplay of factors. These findings further underscore the complexity of the behavioural determinants underlying medication adherence, the challenges involved in effectively targeting them (Yussof et al., 2022), and, consequently, the importance of ongoing research to deepen our understanding and develop more effective solutions. This thesis represents a step in that direction.

Study limitations

This review is not without limitations, which should be carefully considered when interpreting its findings. Although a comprehensive search strategy was applied across four major databases, it is possible that some relevant studies were missed. The exclusion of conference abstracts and grey literature, while methodologically justified by the need for detailed intervention descriptions, may have resulted in the omission of potentially valuable sources. Furthermore, the application of the BCTT may not have fully captured all intervention components. In some cases, techniques may have been employed but not explicitly described in sufficient detail to permit reliable coding. In line with official BCTT coding guidelines (www.bct-taxonomy.com), only clearly stated and well-documented techniques were included in the analysis.

Another important limitation concerns the heterogeneity of adherence measurement across the included studies. Not only were different tools used to assess adherence (e.g., self-reports, electronic monitoring, urine assays), but also the operationalisation of adherence varied substantially. While some studies treated adherence as a continuous variable (Ell et al., 2009; Graetz et al., 2018; Krok-Schoen et al., 2019), others dichotomised it (i.e., adherent vs. non-adherent) using various thresholds:

some set the cut-off at 80% of prescribed doses taken, (Bluethmann et al., 2021; Chalela et al., 2018; Mougalian et al., 2017) others at 90% (Komatsu et al., 2020) or 75% (Sanft et al., 2021), and some relied on self-report instrument scores (Mamguem Kamga et al., 2020; Moon et al., 2019). Moreover, different studies employed related but not entirely interchangeable terms, such as persistence (continuing treatment for the intended duration), discontinuation (prematurely stopping treatment), and compliance (often used synonymously with adherence) (Hadji et al., 2013; Jacob et al., 2015; Mamguem Kamga et al., 2020; Markopoulos et al., 2015; K.-D. Yu et al., 2012; Ziller et al., 2013), which, although conceptually overlapping, can carry distinct implications. These inconsistencies in terminology and measurement approaches inevitably limit the comparability of study results and complicate the synthesis of findings. Additionally, differences in study designs, follow-up durations, and assessment timing further underscore the preliminary nature of the conclusions drawn regarding the effectiveness of specific BCTs.

It is also important to acknowledge that the frequency with which a given technique appears in effective interventions does not in itself constitute definitive evidence of its efficacy. Many of the included studies were pilot or single-arm trials, and the emphasis on statistical significance may be misleading in such contexts. Robust, hypothesis-driven studies are therefore needed to systematically test the assumptions and trends identified in this review.

Lastly, although the inclusion criteria of this review were intended to encompass interventions targeting adherence to all categories of oral anticancer agents, nearly all of the included studies specifically addressed endocrine treatments—except for one focused on oral chemotherapy and targeted therapy (Komatsu et al., 2020). Consequently, the insights and considerations presented in this review predominantly pertain to adherence issues related to endocrine therapy and should not be assumed to apply to other oral anticancer regimens.

Clinical implications

The insights discussed in this review give rise to preliminary yet potentially valuable observations. Future comparative studies specifically designed to test the hypotheses formulated herein may represent a crucial step toward the development of evidence-based guidelines to inform the design of adherence-enhancing interventions for BC patients. In particular, the techniques “feedback on behaviour” and “prompts/cues” emerged as promising components and warrant further empirical evaluation, building on the preliminary investigation carried out in Study 5. Should their effectiveness be confirmed, these BCTs should be carefully considered in the planning of future interventions aimed at improving medication adherence.

Conclusions

This systematic review provides a current and comprehensive overview of the interventions aimed at improving medication adherence among patients with BC. Despite growing efforts in this area, a clear understanding of the behavioural mechanisms influencing adherence remains limited. To address this gap, future studies should aim to clarify why certain interventions succeed while others do not, with particular attention to the role of specific BCTs such as "feedback on behaviour" and "prompts/cues." These techniques appear promising and merit further empirical testing, with the pilot study described in Chapter 4 representing an initial step in that direction. Additionally, to strengthen reproducibility and allow for more robust comparisons across the studies, it is essential that future interventions be described in detail using consistent, standardised terminology, such as that provided by the BCTT. Doing so will not only support transparency in intervention development but also enhance the quality of evidence synthesis in future research efforts (Michie, Abraham, et al., 2011).

3.2 Study 2: A scoping review of adherence predictive models in breast cancer

Having provided, with Study 1, a comprehensive overview of interventions designed to support medication adherence in BC patients. we now turn to the second guiding question of this thesis: how can those most in need of interventions or additional support be identified? To address this issue, Study 2 presents a scoping review focused on predictive models of non-adherence (Pezzolato, Spada, et al., 2023).

As outlined in Chapter 1, predictive modelling has found various applications in healthcare, such as guiding clinical decision-making, predicting disease trajectories, and identifying patients at greater risk (Toma & Wei, 2023). The present scoping review explores its use in relation to medication adherence (Pezzolato, Spada, et al., 2023).

The rationale for conducting this review lies in a key clinical and organisational challenge: offering adherence-support interventions to all BC patients prescribed oral therapy is neither feasible nor cost-effective (Elting & Shih, 2004). Consequently, there is a pressing need to identify those patients most at risk of non-adherence and, therefore, most likely to benefit from targeted support. Predictive models may provide an effective solution to this issue, enabling the implementation of more tailored and efficient intervention strategies.

If properly developed, externally validated on independent samples, and integrated into clinical practice, these models might potentially serve as valuable tools to support

patient assessment (Toma & Wei, 2023). Their possible value could lie in identifying individuals at higher risk of suboptimal treatment adherence, thus enabling, at least in principle, the timely delivery of appropriate support (Merino-Barbancho et al., 2025; Yerrapragada et al., 2021).

In this regard, predictive modelling could represent a potentially useful line of research in the field of medication adherence. To gain a comprehensive understanding of the current state of knowledge, it is not sufficient to consider only the interventions developed to support adherence, as discussed in the previous section; it is equally crucial to explore the predictors of non-adherence and identify the patients most in need of such interventions. This dual perspective allows for a more integrated and nuanced overview of the state of the art in this area of study.

3.2.1 Aims of the study

This study was initially undertaken with the broader aim of identifying, synthesising, and critically examining the existing literature on predictive models developed for three key outcomes in BC care: psychological distress, quality of life, and adherence to medication. In the context of this thesis, however, the focus will be specifically placed on the latter, in line with the overarching research objective. Given the breadth of the research question and the exploratory nature of the investigation, a scoping review design was deemed the most appropriate methodological approach (Munn et al., 2018). Some of the themes identified here are introduced only at a preliminary level, but are examined in greater depth in Study 3, where a systematic review was conducted with a partially overlapping focus.

The primary aim was to provide a comprehensive overview of existing predictive models, outline their characteristics, map the key factors associated with adherence, and assess the studies' risk of bias. By offering a structured synthesis of the available evidence, this review intends to contribute to the advancement of knowledge in this field and support the development of more effective strategies to promote optimal adherence throughout the BC care trajectory.

To the best of our knowledge, this is the first review to systematically explore predictive models of medication adherence in the specific population of BC patients. As such, the findings presented and discussed here offer a valuable resource for both researchers and HCPs engaged in BC care.

3.2.2 Material and methods

The methods described in this section reflect the broader scope of the scoping review, which covered predictive models of adherence, quality of life, and psychological

distress. In this thesis, only adherence-related findings are reported; results on the other outcomes are detailed in the original publication (Pezzolato, Spada, et al., 2023).

Search strategy

A literature search was carried out in January 2023 to identify studies that developed or applied predictive models for the outcomes of interest (i.e., quality of life, psychological distress, or medication adherence) in patients with BC. Searches were conducted across three online databases: PubMed, Embase, and Scopus. A search string was developed by combining terms related to three core concepts: (1) BC, (2) predictive or prognostic models, and (3) relevant psychological outcomes (i.e., quality of life, depression, anxiety, distress, or adherence). The complete search string is available in Appendix 1. No restrictions were applied regarding the publication date.

Inclusion and exclusion criteria

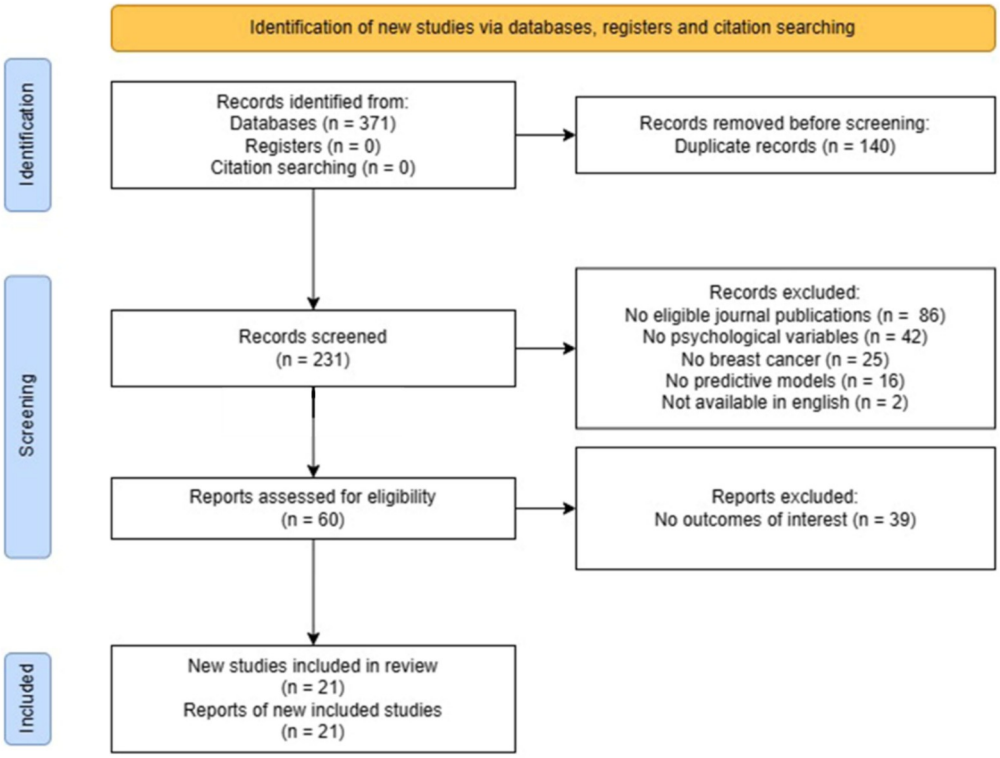
To be eligible for inclusion, studies had to meet the following criteria: (1) the sample consisted of BC patients; (2) a predictive model was either developed or applied; (3) at least one of the outcomes of interest was among the model's targets; (4) the paper was published in English. Studies that focused exclusively on medical outcomes or that did not report any of the outcomes of interest were excluded.

Screening

The screening and selection process followed the PRISMA-ScR (PRISMA extension for Scoping Reviews) guidelines (Tricco et al., 2018). A total of 371 records was initially identified. After removal of duplicates, 231 unique articles were screened based on title and abstract. Abstracts, commentaries, editorials, letters, proposals, meta-analyses, and review articles were excluded. This led to the exclusion of 171 articles, leaving 60 for full-text screening.

Screening was independently performed by two authors and discrepancies between reviewers were resolved by a third author. Ultimately, 21 studies met the inclusion criteria and were included in the analysis, of which six specifically focused on predictive models of medication adherence. The selected articles were jointly reviewed and approved for inclusion by multiple authors. Further details on the screening process are provided in Figure 2.

Figure 2. *PRISMA flow diagram of the study selection process for Study 2.*



Adapted from Pezzolato et al., Patient Preference and Adherence, 2023.

Risk of bias assessment

The risk of bias was not carried out in the original published study (Pezzolato, Spada, et al., 2023); however, it was performed specifically for this doctoral thesis to allow a deeper examination of the included studies and to strengthen the overall solidity and methodological rigour of the work. The risk of bias was assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST) (Moons et al., 2019). This tool evaluates potential bias across four domains (participants, predictors, outcome, and analysis) through 20 signalling questions, and also examines concerns related to the applicability of the models in terms of participants, predictors, and outcome.

3.2.3 Results

Summary of study characteristics

The six studies included in this review proposed predictive models of medication adherence among BC patients (Cahir et al., 2017; Henry et al., 2012; Kuo et al., 2022; Meneveau et al., 2020; Shinn et al., 2022; Yanez et al., 2021). Each of them examined adherence to oral endocrine therapy, with some focusing on specific dimensions such as treatment discontinuation or persistence, in line with what was observed in Study 1.

The performance of the predictive models was assessed using metrics such as the area under the receiver operating characteristic curve (AUC) and hazard ratios. Among the included studies, only Meneveau et al. (Meneveau et al., 2020) applied a held-out validation set to validate their model, while none reported any process of external validation.

A detailed overview of studies characteristics is presented in Table 4.

Table 4. *Original research studies on the prediction of adherence and treatment discontinuation: characteristics and results.*

First author, year	Sample	Study design	Predictive model	Outcomes	Predictors	Validation	Results
Cahir, 2017	BC, stage I-III 3,415	Retrospective cohort study	Multivariate relative risks model	Non-persistence	Demographic, clinical, and treatment-related factors	N.a.	Women aged <50 years and prescribed antidepressants resulted at greater risk, while married women and those with previous use of medications had lower risk. However, the model has limited predictive ability (AUC = 0.61).
Henry, 2012	BC, stage I-III 503	Randomized controlled trial	Univariate and multivariate analysis of predictors	Discontinuation	Demographics, clinical, and treatment-related factors	N.a.	Younger age (HR, 1.4; 95% CI, 1.0 to 1.9; *p* = 0.04), taxane-based chemotherapy (HR, 1.9; 95% CI, 0.99 to 3.6; *p* = 0.048), and pre-existing pain (HR, 1.1; 95% CI, 1.0 to 1.2; *p* = 0.04) predicted aromatase inhibitors discontinuation.

First author, year	Sample	Study design	Predictive model	Outcomes	Predictors	Validation	Results
Kuo, 2022	BC, stage n.a. 385	Retrospective cohort study	Multiple logistic regression, decision tree and artificial neural networks	Medication-taking behaviour	Demographic, clinical, and treatment-related factors	N.a.	The top five predictors of lower adherence were duration of AET discontinuation, duration of AET use, younger and older age, lower BMI, and radiotherapy.
Menevea u, 2020	BC, stage I 11,037	Retrospective cohort study	Stepwise selection and logistic regression	Adherence and medication initiation	Comorbidities, socio-economic factors, prescription medications, and demographics	Internal (held-out validation set)	The models have limited predictive ability (AUC = 0.65-0.60).
Shinn, 2022	BC, stage I-III 82	Prospective study	Discrete decisional logic applied to a behavioural feedback network	Discontinuation	Patient-related factors, patient-provider relationship, treatment, and comorbidities	N.a.	Low risk perception, below-median QoL, low AET-related side effects, low level of cancer recurrence worry, and median levels of general anxiety where associated with discontinuation.*
Yanez, 2021	BC, stage n.a. 954	Randomized clinical trial (post hoc analysis)	Cox proportional hazards regression	Discontinuation	Comorbidities and QoL	N.a.	Prior chemotherapy (HR, 0.57; 95% CI, 0.35-0.92; p = 0.02) and older age (HR, 0.23-0.40; 95% CI, 0.07-0.86; p = 0.001-0.02) were associated with a lower probability of early discontinuation. Depression (HR, 1.82; 95% CI, 1.19-2.77; p = 0.005) and poor social (HR, 1.94; 95% CI, 1.20-3.13; p = 0.006)

						and physical well-being (HR, 2.12; 95% CI, 1.30-3.45; p = 0.002) were identified as significant modifiable risk factors for early discontinuation.

AET = adjuvant endocrine therapy; AUC = area under the receiver operating characteristic curve; BMI = body mass index; CI = confidence interval; HR = hazard ratio; n.a. = not available; QoL = quality of life;.
** No predictive values are available.*

Synthesis of results

The methodologies adopted across the included studies varied considerably, encompassing multivariate binomial models (Cahir et al., 2017), logistic regression analyses (Kuo et al., 2022; Meneveau et al., 2020), decisional logic frameworks based on behavioural feedback networks (Shinn et al., 2022), and Cox proportional hazards models (Henry et al., 2012; Yanez et al., 2021).

These investigations examined demographic, clinical, treatment-related, psychological, and behavioural factors as potential predictors of non-adherence. More specifically, all included studies assessed at least some demographic factors, such as age, ethnicity, and socioeconomic status, as well as clinical or treatment-related variables, including comorbidities, side effects, and type of treatment received. Psychosocial factors, such as depression, anxiety, and quality of life, were included as candidate predictors in only half of the studies (Meneveau et al., 2020; Shinn et al., 2022; Yanez et al., 2021), and behavioural factors such as refill routine, previous discontinuation, and adherence to other treatments were also examined in only three studies (Kuo et al., 2022; Meneveau et al., 2020; Shinn et al., 2022). From a demographic perspective, age was consistently included as a candidate predictor and was significantly associated with adherence in all included studies, with the exception of one (Shinn et al., 2022). Younger age was most often linked to poorer adherence (Cahir et al., 2017; Henry et al., 2012; Yanez et al., 2021), although in one case both younger and older age groups were at higher risk (Kuo et al., 2022). Several clinical and treatment-related characteristics were associated with suboptimal adherence. Pain symptoms, for example, were significantly linked to lower adherence in both studies that examined them (Henry et al., 2012; Meneveau et al., 2020). Taxane-based chemotherapy showed the same pattern in the single study assessing it (Henry et al., 2012). Low endocrine therapy side effects were associated with non-adherence in one of the two studies investigating this factor (Shinn et al., 2022), as was lower body mass index

(Kuo et al., 2022). Prior radiotherapy was linked to reduced adherence in one out of the three studies that included it (Kuo et al., 2022), while the absence of prior chemotherapy emerged as a significant predictor of non-adherence only once out of five examinations (Yanez et al., 2021). Psychological and cognitive factors were also found to be influential. Poor quality of life was associated with lower adherence in both studies that examined it (Shinn et al., 2022; Yanez et al., 2021), while low perceived risk and limited concern about cancer recurrence showed the same pattern in the single study assessing these factors (Shinn et al., 2022). Depression and generalised anxiety were each associated with lower adherence in one out of the two studies that investigated them (Shinn et al., 2022; Yanez et al., 2021). Finally, behavioural factors such as the duration of oral medication use and the duration of previous treatment discontinuations were also associated with lower adherence in the single study that examined them (Kuo et al., 2022).

It is worth noting that two of the reviewed models demonstrated limited predictive accuracy, as reflected by their low AUC values (Cahir et al., 2017; Meneveau et al., 2020), suggesting that further refinement is needed to enhance their clinical applicability.

Risk of bias

Table 5 provides a summary of the risk of bias and applicability assessments.

All studies were rated as having a high overall risk of bias, based on the PROBAST tool (Moons et al., 2019). According to PROBAST guidelines, a high risk in any individual domain results in an overall high-risk classification. In these cases, the elevated overall risk stemmed primarily from concerns within the analysis domain, which evaluates the appropriateness of statistical methods and analytical procedures.

More specifically, the signalling questions that proved most problematic within the analysis domain were those concerning the handling of continuous predictors, the appropriate evaluation of model performance, and the consideration of overfitting and optimism in performance estimates. All included studies were judged not to have handled continuous predictors appropriately, as each categorised at least some continuous variables (e.g., age, Body Mass Index, Charlson Comorbility Index). Such categorisation leads to a loss of relevant information and reduces models' predictive ability, and is therefore discouraged by PROBAST (Moons et al., 2019).

Notably, only one of the included studies (Cahir et al., 2017) reported calibration analyses in addition to discrimination, thereby meeting the key requirements for a thorough assessment of model performance. Calibration is crucial to determine how closely predicted risks correspond to observed outcomes; without it, predicted probabilities may be misleading and undermine the models' clinical usefuness,

potentially leading to suboptimal decision-making (Alba et al., 2017; Moons et al., 2019).

Moreover, none of the included studies reported the use of internal validation methods such as bootstrapping and cross-validation, which are essential for quantifying model overfitting and optimism in predictive performance. The only exception was the study by Meneveau et al. (Meneveau et al., 2020), which conducted internal validation by splitting the dataset into training, validation, and test sets. However, this approach still did not meet PROBAST requirements, as such split-sample validation is not considered sufficient to adequately account for optimism in predictive performance.

Finally, only one study was assessed as presenting a high risk of bias within the predictors domain, which evaluates the selection and measurement of predictors and their potential to introduce bias. Kuo et al. (Kuo et al., 2022) identified the duration of therapy discontinuation and duration of medication use as the most influential predictors in their model. However, these variables are inherently unavailable at the start of treatment, limiting the model's applicability if intended for use at the initiation phase. Relying on post-treatment variables for early prediction undermines the model's prospective utility and raises methodological concerns.

Table 5. *Risk of bias assessment – Prediction Model Risk of Bias Assessment Tool (PROBAST)*

First author, year					Applicability concerns			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Cahir, 2017	Low	Low	Low	High	Low	Low	Low	High	Low
Henry, 2012	Low	Low	Low	High	Low	Low	Low	High	Low
Kuo, 2022	Low	High	Low	High	Low	Low	Low	High	Low
Meneveau, 2020	Low	Low	Low	High	Low	Low	Low	High	Low
Shinn, 2022	Low	Low	Low	High	Low	Low	Low	High	Low
Yanez, 2021	Low	Low	Low	High	Low	Low	Low	High	Low

RoB = risk of bias.

3.2.4 Discussion

This scoping review provided a comprehensive overview of studies that developed predictive models for medication adherence, enabling the identification of key determinants and the characterisation of the main features of these models. All the included studies focused specifically on endocrine therapy, which is consistent with the findings of the previously discussed systematic review (Pezzolato, Marzorati, et al., 2023), highlighting the particular attention devoted to this class of treatments in adherence research. This emphasis is well justified, as endocrine therapies are typically administered orally and over prolonged periods, often spanning five to ten years, placing the responsibility for correct and consistent intake primarily on the patients themselves (Greer et al., 2016).

Demographic, clinical, treatment-related, psychological, and behavioural variables emerged as significant predictors of non-adherence across the studies reviewed (Cahir et al., 2017; Henry et al., 2012; Kuo et al., 2022; Meneveau et al., 2020; Shinn et al., 2022; Yanez et al., 2021). Of note, depressive symptoms were found to be associated with a higher likelihood of non-adherence (Cahir et al., 2017; Yanez et al., 2021), aligning with prior evidence (Yussof et al., 2022).

Several of the predictors included in the reviewed models, such as demographic characteristics, medical history, and treatment-related variables, are routinely collected in clinical practice, making them readily accessible for use in risk assessment. These elements can thus be integrated with relative ease into existing workflows to support early identification of patients who may be more vulnerable to non-adherence. In contrast, other relevant factors, such as illness representations, concerns about cancer recurrence, emotional distress (including anxiety and depressive symptoms), and social well-being, are not commonly recorded in standard health records. Incorporating the assessment of these psychosocial dimensions into routine evaluations could contribute to a more comprehensive understanding of patient profiles and support the development of more accurate predictive models.

It is also important to highlight that two of the included studies reported limited predictive accuracy for their adherence models (Cahir et al., 2017; Meneveau et al., 2020). This further underscores the inherently multifaceted nature of medication-taking behaviour, which is shaped by a complex interplay of factors and deeply rooted in patients' individual experiences and perceptions (Pinheiro et al., 2017; Yussof et al., 2022). Consequently, adherence remains particularly difficult to predict, even when models incorporate a broad range of potential predictors. The multiplicity of factors influencing patients' adherence also makes it challenging to design effective interventions, as no single approach can adequately address such complexity. This may help explain the findings of Study 1 (Pezzolato, Marzorati, et al., 2023), where

only 35% of the interventions reviewed proved to be effective. Coherently, the intervention developed within this doctoral project and pilot tested in Study 5 adopts a multi-component approach, with its three components designed to target different determinants of non-adherence.

However, even among those models reporting satisfactory performance indicators, their predictive accuracy should be interpreted with caution. Indeed, performance metrics alone are not enough to establish a model's clinical utility and should be considered in conjunction with other parameters to ensure both reliability and applicability in real-world settings (Seneviratne et al., 2020; N. H. Shah et al., 2019). A predictive model, no matter how accurate, offers limited value if its outputs do not lead to actionable clinical strategies or if its implementation proves impractical or economically unsustainable (Seneviratne et al., 2020).

Even before considering model implementation, it is important to note that all the included studies were judged to be at high risk of bias. This raises important concerns about their validity and appropriateness of their potential use in clinical settings. In particular, the lack of calibration and adequate internal validation, together with the common practice of categorising continuous variables, casts doubt on the actual predictive capacity of these models (Alba et al., 2017; Moons et al., 2019). Addressing these sources of bias is essential, as the application of biased predictive models in clinical contexts may lead to unsafe or inefficient decision-making, resulting in wasted resources or even harm to patients (G. S. Collins et al., 2024; Moons et al., 2019; Seneviratne et al., 2020).

In summary, the potential of these models to support the early identification of patients at greater risk of poor adherence, and thereby inform more timely and tailored interventions, still seems far from being realised. One might legitimately ask whether more powerful ML-based predictive models could help overcome the challenges discussed here. ìThis question is addressed in the systematic review presented in Study 3, which examined the contribution of AI to medication adherence in BC and included a detailed analysis of studies developing ML-based predictive models. Several themes first introduced here, such as the implementation gap and the challenges surrounding the clinical utility of predictive models, are taken up again and explored in greater depth in the following sections (Study 3).

Study limitations

This work is not without limitations, which should be taken into account when interpreting the findings. Firstly, the considerable variability among the studies included in this review, both in terms of methodological approaches and characteristics, may limit the overall interpretability and comparability of the results.

The predictive models were built using different statistical strategies and performance was assessed through diverse metrics. Moreover, two of the reviewed studies (Henry et al., 2012; Yanez et al., 2021) did not report specific measures of predictive accuracy, limiting their analyses to statistical associations (i.e., hazard ratios); therefore, their findings should be interpreted with caution. This issue align with observations made by Varga et al. (Varga et al., 2020), who pointed out that many studies labelled as "predictive" in fact rely solely on correlational analyses, potentially leading to misleading conclusions. Nonetheless, the inclusion of this two studies was deemed useful as it contributes to a more comprehensive overview of the current state of the art. Moreover, by explicitly aiming to identify predictors of non-adherence, both studies offer insights that are pertinent to the scope of this review.

Further complexity is introduced by the different strategies adopted to assess adherence, ranging from medication possession ratios to clinical records and telephone interviews, and by the broad disparity in sample sizes across studies, which spanned from 82 to 11.037 participants. These factors further limit the possibility of drawing generalisable conclusions.

A further limitation emerged in light of the findings from Study 3, namely that the search strategy used for this scoping review was not sufficiently inclusive to capture all relevant studies. For instance, at least two works (Kaur et al., 2021; Yerrapragada et al., 2021), both developing ML-based predictive models, were not retrieved because their titles and abstracts did not include expressions such as "predictive model" or "prediction model" that our search string required (see Appendix 1). This indicates that our strategy excluded some pertinent studies and should have been broader. Nevertheless, these studies are fully reported and discussed in Study 3.

Clinical implications

Psychological interventions have demonstrated efficacy in supporting the emotional well-being and overall quality of life of individuals with BC (Hwang et al., 2023; Lai et al., 2021). In addition, research suggests that such interventions may also alleviate physical symptoms, including pain and fatigue (Abrahams et al., 2020; Johannsen et al., 2013; Wong et al., 2023), and contribute to improved adherence to prescribed therapies (Arch et al., 2022; Ream et al., 2021). However, extending these services to the growing population of BC patients presents challenges in terms of feasibility and cost-effectiveness (Elting & Shih, 2004). In this context, the predictive models analysed in this review might represent a potentially useful approach for more efficiently targeting psychological interventions. By helping to identify individuals who may be at greater risk of non-adherence, such models could, in principle, support the

development of more timely and tailored interventions, with the possible benefit of optimising outcomes and reducing unnecessary healthcare expenditure.
However, realising this potential requires overcoming the observed risks of bias and the current implementation gap—namely, the disconnect between model development and their practical integration into clinical settings (Seneviratne et al., 2020; Watson et al., 2020). This process involves not only adequate validation and calibration of the models but also adaptation to routine workflows.
Moreover, the multiplicity of factors identified in predictive modelling studies suggests that non-adherence is unlikely to be effectively addressed through single-approach interventions. Instead, it calls for multi-component and personalised strategies, tailored to counteract the specific set of non-adherence determinants identified within a given population or in individual patients.
In summary, the overview provided here may serve as a useful reference for clinicians and researchers working on the design and implementation of psychological support strategies in oncology, offering a synthesis of the current landscape and identifying key areas where further progress is warranted.

Conclusion
The predictive models reviewed in this work could potentially serve as valuable tools for the early identification of BC patients who are more likely to benefit from targeted psychological interventions. However, important methodological limitations place them at risk of bias and hinder this potential. To address these limitations, clinicians and researchers are encouraged to further validate and calibrate these models to ensure their robustness and applicability in real-world clinical settings. Their effective integration into routine clinical practice could enable the timely detection of patients at high risk of non-adherence, thus paving the way for prompt and personalised support strategies aimed at improving both adherence and overall patient outcomes.
The crucial topic of predictive model implementation has been introduced in this section and will be explored in greater depth in the next, which presents Study 3.
In addition, the findings reported here highlight the need for multi-component interventions to more effectively support medication adherence, a direction that was preliminarily explored through the pilot study presented in Study 5.

3.3 Study 3: Artificial intelligence to predict, monitor, and support adherence among breast cancer patients

The topic of AI is attracting growing scientific and clinical interest, with applications in healthcare that are broad-ranging and cross-disciplinary (Al Kuwaiti et al., 2023; Bajwa et al., 2021). The decision to carry out the systematic review presented in this

section (Pezzolato et al., 2025) arises from the need to investigate whether, and in what ways, AI technologies are being employed to support medication adherence in BC patients. Furthermore, the findings of Study 2 raised open questions concerning the clinical utility of predictive models of adherence. Given that this represents one of the main areas where AI, particularly in the form of ML, has been applied, we sought to explore whether such models could harness the computational power of AI to yield more robust and clinically meaningful results.

As will be discussed, the findings of the review indicate that AI is currently applied primarily to the development of ML predictive models of medication adherence. By systematically reviewing studies focused on the development of predictive models, this analysis builds upon and extends the previous review (Study 2), shifting the focus specifically toward ML-based approaches. The use of PROBAST (Moons et al., 2019) enabled a more in-depth assessment of the models' methodological quality, enhancing our understanding of the current state of the field and helping to identify critical gaps that warrant further investigation.

Importantly, the scope of the review was not limited to ML predictive models alone. It also considered AI-based interventions designed to directly support medication adherence, such as conversational agents or digital platforms. Although only one study describing such an intervention was identified, it nonetheless offers valuable insights and serves as a useful point of reflection for future research and development.

As illustrated in the findings, AI emerges as a potentially innovative element capable of advancing both key lines of research discussed in the previous sections: the development of adherence-supporting interventions and of predictive models for non-adherence. However, the integration of AI technologies into healthcare settings is not without challenges. It raises important considerations related to ethical standards, patient safety, and clinical reliability. These issues warrant careful reflection and will be addressed in detail in the following sections.

3.3.1 Aims of the study

This systematic review aims to provide a thorough synthesis of how AI has been employed to address medication non-adherence in patients with BC. To the best of our knowledge, no previous reviews has encompassed the full spectrum of AI applications targeting this issue within this specific population. In addition to mapping existing approaches, the review also outlines key areas for future research and reflects on the ethical and practical challenges that remain to be addressed.

3.3.2 Material and methods

This systematic review was carried out following the PRISMA guidelines (Page et al., 2021). It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number: CRD42024587020. A formal protocol for the review was not developed.

Search strategy

A search strategy combining keywords related to three central concepts, (1) adherence, (2) BC, and (3) AI, was developed and applied across three databases: Scopus, Embase, and PubMed. The complete search string is available in Appendix 1. The search included studies published up to January 15, 2025.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they: (1) focused on any AI technology (e.g., ML, DL, NLP, generative AI) applied to predict, monitor, or support adherence to oral medication; (2) included a sample of BC patients; (3) were published in English; and (4) had full-text available online. Reviews, conference abstracts, and editorials were excluded, as were studies involving mixed patient populations where outcomes specific to BC patients could not be separately identified.

Screening

The screening process was conducted using Rayyan software, a web and mobile platform designed for systematic reviews (Ouzzani et al., 2016). Two researchers independently performed both title/abstract and full-text screening in blinded mode, meaning they were unaware of each other’s selections. Following the initial screening, the authors reviewed the full texts of all studies that met the inclusion criteria to confirm their eligibility. Any discrepancies were referred to a third author, and disagreements were resolved through discussion until consensus was reached.

Risk of bias assessment

For studies involving the development of ML predictive models, the risk of bias was assessed using PROBAST (Moons et al., 2019). This tool evaluates potential bias across four domains (participants, predictors, outcome, and analysis) through 20 signalling questions, and also examines concerns related to the applicability of the models in terms of participants, predictors, and outcome.

For the study focused on the implementation of an intervention supporting BC patients, risk of bias was evaluated using the previously cited Downs and Black's

methodological quality scale (Downs & Black, 1998) (for a brief description of this tool, see section 3.1.3).

The bias assessments were independently conducted by two authors, with any disagreements resolved through discussion until consensus was reached.

Data extraction and summary

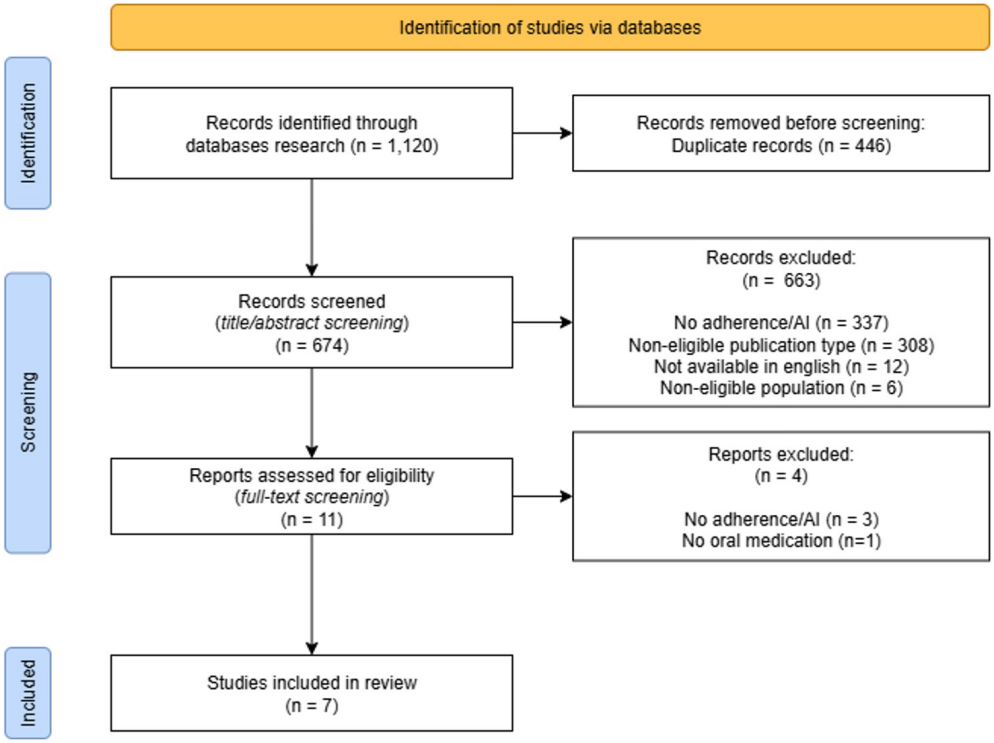
For each included study, key information and findings were extracted and recorded in an Excel spreadsheet. Extracted variables included authors, title, publication year, country, study design, objectives, sample size, AI subtypes and algorithms, adherence measurement methods, and results. For studies focusing on the development of ML predictive models, additional data on predictors, performance metrics, and validation types were also collected. Data extraction was performed independently by two authors and subsequently verified by two other researchers.

3.3.3 Results

Summary of study characteristics

A total of 1,120 records emerged from the initial database search. Following the removal of duplicates and initial screening based on titles and abstracts, 11 articles were deemed potentially relevant. Of this, seven satisfied all the inclusion criteria and were retained for analysis (see Figure 3 for the summary of the selection process).

Figure 3. *PRISMA flow diagram of the study selection process for Study 3.*



The final set of studies, published between 2019 and 2024, was geographically diverse: four originated from Europe (three from France and one from Italy), two from the USA, and one from Taiwan. While some studies focused specifically on early-stage (n = 2) or metastatic BC (n = 2), the others did not report disease stage. Sample sizes varied substantially, ranging from 32 to 229,695.

Adherence was assessed through different methodologies: three studies used administrative health data or medical records, three relied on self-reported information, and one employed electronic medication monitoring systems.

Six of the seven studies concentrated on the development of ML models to predict adherence behaviours (five employed retrospective cohort designs, and one described the protocol of a randomised controlled trial). Only one study took a prospective approach, presenting an AI-driven intervention aimed at improving adherence to oral therapies.

A summary of the main features of the included studies is provided in Table 6.

Table 6. *Characteristics of the studies included in Study 3.*

Author	Year	Title	Country	Design	Aim	Sample	AI technologies / Algorithms	Adherence measure	Predictors	Performance metrics	Validation	Intervention	Results
Balazard et al.	2023	Adjuvant endocrine therapy uptake, toxicity, quality of life, and prediction of early discontinuation	France	Retrospective cohort study	To describe real-world patterns of ET uptake including discontinuations, toxicities, and QoL up to 5 years from initiation and to develop a prediction model of early discontinuation.	BC, stage I-III (descriptive analyses, *n* = 6,488; model development, *n* = 5,282; training set, *n* = 4,225; validation set, *n* = 1,057)	ML / L2-penalized Cox regression and gradient boosted trees with a Cox partial likelihood	Patients' self-declarations recorded in electronic case report forms.	Discontinuation of ET, QoL, physical functioning, role functioning, social functioning, emotional functioning, cognitive functioning scores, mastectomy and radiotherapy, fatigue, pain, dyspnea, insomnia, systemic therapy side effects, breast symptoms, and arm symptoms.	C-indexes (0.60 – 0.64).	Internal (nested cross-validation, held-out validation set)	N.a.	25 variables were significantly associated with early discontinuation. Patients who have already discontinued an ET after primary treatment were more likely to discontinue ET definitively; higher QoL, physical functioning, role functioning, social functioning, emotional functioning, cognitive functioning scores, and receiving mastectomy and radiotherapy were associated with lower rates of early ET discontinuation; fatigue, pain, dyspnea, insomnia, systemic therapy side effects, breast symptoms, and arm symptoms were associated with a higher rate of early ET discontinuation.
Chaix et al.	2019	When chatbots meet patients: One-year prospective study of conversations between patients with breast cancer and a chatbot	France	Prospective study	To evaluate one year of conversations between patients with BC and a chatbot.	BC, stage n.a. (*n* = 958; Adherence measurement, *n* = 33)	ML / n.a.	Answers to the chatbot's reminder messages were recorded and used to measure adherence rates.	N.a.	N.a.	N.a.	A chatbot that interacts with users by simulating a human conversation through text was designed to empower patients and answer their questions with personalized insights.	The overall satisfaction was 93.95% (900/958). The authors reported that the average compliance of patients using the medication reminder feature improved by more than 20%.
Kaur et al.	2021	Theory-guided randomized neural networks for decoding medication-taking behaviour	USA	Retrospective cohort study	To predict daily medication-taking behaviour based on survey data over 3 time points (baseline, 4 months, 8 months).	BC, stage I-III (*n* = 32)	ML / randomized neural networks	Medication event monitoring system.	Survey data regarding BC survivorship knowledge, medication attitudes, medication self-efficacy, QoL, and other factors.	Overall accuracy and individual accuracy ($0.92 < OA < 0.97$).	N.a.	N.a.	The proposed model outperforms existing computational models in terms of prediction accuracy under conditions of randomness. It was able to predict the randomness of the subjective values and decision rules that contribute to the dynamics of patients' medication-taking behaviour.
Kuo et al.	2021	Using data mining technology to predict medication-taking behaviour in women with breast cancer: A retrospective study	Taiwan	Retrospective cohort study	To predict the influencing factors of long-term AHT adherence and persistence.	BC, stage n.a. (*n* = 385)	ML / decision tree and artificial neural networks	Clinical registry and medical records (MPR > 80%).	The top five influencing factors were duration of AHT discontinuation, duration of AHT use, age at diagnosis, body mass index, and receipt of radiotherapy.	Overall accuracy, specificity, sensitivity, and AUC (0.90 – 1.00).	N.a.	N.a.	All three models achieved high classification performance. Multiple logistic regression was the most effective approach (accuracy: 96.37%; specificity: 96.75%; sensitivity: 96.12%).

Author	Year	Title	Country	Design	Aim	Sample	AI technologies / Algorithms	Adherence measure	Predictors	Performance metrics	Validation	Intervention	Results
Masiero et al.	2023	A machine learning model to predict patients' adherence behaviour and a decision support system for patients with metastatic breast cancer: protocol for a randomized controlled trial	Italy	RCT protocol	To evaluate the effectiveness of a decision support system and a ML web application in promoting adherence to oral anticancer treatments and to collect a set of new physical, psychological, social, behavioural, and QoL predictive variables to refine the preliminary version of the predictive ML model.	mBC (RCT, *n* = 100; retrospective data for the predictive model, *n* = 2,750)	ML, NLP / Shapley values	Weekly medication diaries and self-report measures.	Sociodemographic variables, diagnosis, biochemical and medical tests, procedures and medical history, treatment programs, treatment side effects, comorbidities, and familiarities, initiation of the treatment interruption, and skipped treatment doses. The RCT will allow the addition of the following variables as predictors to the predictive model: personality traits, self-efficacy for coping with cancer, sense of coherence, pain, anxiety, depression, risk perception, and QoL.	AUC, precision, recall, sensitivity, specificity, κ, and positive and negative predictive values.	N.a.	Participants in the intervention group will have access to a web-based decision support system, and a ML-based application will be used in shared decision-making sessions.	N.a.
Rinder et al.	2024	Dynamic projection of medication non-persistence and non-adherence among patients with early breast cancer	France	Retrospective cohort study	To model persistence and adherence to oral anticancer treatment.	eBC (*n* = 229,695)	Deep learning / gated-recurrent unit network, feed-forward neural network, Shapley additive explanations	Administrative health data (MPR > 80%).	Age (> 70 years), past non-adherence, taking more than 1 treatment in the previous 3 months, and low income were predictors of non-persistence. The predictors of non-adherence were similar, adding age (< 50 years) and irregular intervals in treatment purchases.	AUC (0.71 – 0.73).	Internal (held-out validation set)	N.a.	The model was able to estimate the risk of non-persistence and non-adherence among French female patients with localized BC and identified that some factors (age, past behaviour, and number of treatments) may be associated with risk of non-persistence and non-adherence.

Author	Year	Title	Country	Design	Aim	Sample	AI technologies / Algorithms	Adherence measure	Predictors	Performance metrics	Validation	Intervention	Results
Yerrapragada et al.	2021	Machine learning to predict tamoxifen nonadherence among US commercially insured patients with mBC	USA	Retrospective cohort study	To predict tamoxifen non-adherence in the first year after treatment initiation using ML algorithms trained on pretreatment real-world data, to identify predictive baseline factors, and to evaluate administrative data for the development of a non-adherence screening tool.	mBC (*n* = 3,022)	ML / logistic regression, boosted logistic regression, random forest, and feed-forward neural network models	Administrative health data (MPR > 80%).	Patient features (55 years or older at treatment start, receiving care in the South, being a surviving spouse), pretreatment procedures (lymphatic nuclear medicine, radiation oncology, arterial surgery, microbiology, and imaging) or therapy (beta-blockers, antidepressants, and stimulants), and baseline comorbid diagnoses (upper respiratory disease, breathing abnormality, dorsopathy, neurotic disorders, cerebrovascular disease, abdominal pain, and genital disorders)	AUC (0.61 - 0.64), F-score (0.59 - 0.62), sensitivity, specificity.	Internal (cross-validation)	N.a.	All models had moderate predictive accuracy. Logistic regression (AUC 0.64) was interpreted with 94% sensitivity (95% CI, 89 to 92) and 0.31 specificity (95% CI, 29 to 33). The model accurately classified adherence (negative predictive value 89%) but failed in discriminating non-adherence (positive predictive value 48%).

AHT = adjuvant hormonal therapy; AUC = area under the receiver operating characteristic curve; BC = breast cancer; eBC = early-stage breast cancer; ET = endocrine therapy; mBC = metastatic breast cancer; ML = machine learning; MPR = medication possession ratio; N.a. = not available; NLP = natural language processing; OA = overall accuracy; QoL = quality of life; RCT = randomized controlled trial.

Predictive models

The majority of the selected studies (*n* = 6) focused on the development of ML models designed to predict non-adherence in BC patients (Balazard et al., 2023; Kaur et al., 2021; Kuo et al., 2022; Masiero et al., 2023; Rinder et al., 2024; Yerrapragada et al., 2021). These models rely on various patient-related data to estimate the likelihood of future difficulties in medication-taking behaviour over the course of treatment.

Among them, only one study (Balazard et al., 2023) employed regression-based approaches, treating adherence as a continuous outcome by estimating the time interval between treatment initiation and discontinuation. The remaining studies adopted classification frameworks, treating adherence as a binary or categorical variable and aiming to identify patients at increased risk of non-adherence.

A variety of ML techniques were employed. For example, Balazard et al. developed and compared two distinct modelling approaches: an L2-penalized Cox regression and a gradient boosting method optimised via a Cox partial likelihood. Both models demonstrated comparable levels of accuracy, with concordance indices (C-index) ranging from 0.60 to 0.64. Internal validation was carried out through nested cross-validation on the training dataset, and the best-performing model was subsequently evaluated using a separate validation set (Balazard et al., 2023).

Yerrapragada et al. (Yerrapragada et al., 2021) explored four different ML approaches (logistic regression, boosted logistic regression, random forest, and a feedforward neural network) to predict medication non-adherence. These models underwent internal validation through 10-fold cross-validation and yielded limited predictive performance, with AUC values between 0.61 to 0.64 and F1-scores ranging from 0.59 to 0.62 (Carter et al., 2016). To address class imbalance, the authors applied the synthetic minority oversampling technique in a post hoc phase. After retraining, model performance improved substantially, particularly for the random forest model (AUC = 0.93, F1 = 0.78) and the neural network (AUC = 0.79, F1 = 0.71).

In another study, Kuo et al. (Kuo et al., 2022) implemented an ensemble approach combining three distinct algorithms: multiple logistic regression, decision trees, and artificial neural networks. All models achieved high levels of accuracy, with AUCs ranging from 0.90 to 1.00 and classification accuracy between 92.29% and 96.37%. However, the study did not clarify whether any form of validation, such as cross-validation or external testing, was employed to assess the generalisability of the models.

Kaur et al. (Kaur et al., 2021) developed a randomised neural network and compared its predictive accuracy (both at the aggregate and individual levels) with that of a standard neural network architecture. The randomised model showed superior performance, reaching overall and individual accuracy scores exceeding 0.92.

However, the study did not provide evidence of either internal or external validation. The authors acknowledged this limitation and stated their intention to employ a leave-one-subject-out cross-validation strategy in future evaluation.

Rinder et al. (Rinder et al., 2024), on the other hand, constructed a DL model that integrated a recurrent neural network with a feedforward neural network to predict medication adherence and persistence. The model achieved AUC scores of 0.71 for predicting persistence and 0.73 for adherence. Internal validation was conducted using a dataset split into training (60%), validation (20%), and testing (20%) subsets. Additionally, the authors used Shapley Additive Explanations (SHAP) to interpret the model's outputs and identify the most influential predictive features.

Masiero et al. (Masiero et al., 2023) developed ML models aimed at predicting non-adherence in patients with mBC, which are currently being tested within the framework of a randomised controlled trial. The models were built by applying NLP techniques to data extracted from electronic health records and are designed to be refined with new patient data during the course of the trial. Although the authors mention that multiple performance metrics were used to assess the models (such as AUC, precision, recall, sensitivity, specificity, Cohen's kappa, and positive and negative predictive values), specific results were not disclosed. For model interpretability, the authors employed Shapley values, which offer insights into the individual contribution of each risk factor to the model's prediction.

Predictors of non-adherence

The studies included in the review that focused on ML-based predictive models identified a broad range of factors associated with non-adherence, which can be grouped into four main categories: (1) clinical, disease-, and treatment-related factors; (2) behavioural factors; (3) psychosocial factors; and (4) sociodemographic factors.

Within the clinical, disease-, and treatment-related domain, non-adherence was linked to the presence of symptoms or adverse effects (Balazard et al., 2023), complex treatment regimens (Rinder et al., 2024; Yerrapragada et al., 2021), comorbid conditions (Yerrapragada et al., 2021), and lower body mass index (Kuo et al., 2022). Some findings regarding treatment history were inconsistent. For instance, prior exposure to radiotherapy or diagnostic imaging was linked to poorer adherence in one study (Yerrapragada et al., 2021), whereas another associated recent mastectomy or radiotherapy with improved adherence levels (Balazard et al., 2023).

Behavioural factors predictive of non-adherence included past patterns of non-adherence (Balazard et al., 2023; Rinder et al., 2024), a longer elapsed time since

treatment initiation, and more extended previous discontinuation episodes (Kuo et al., 2022).

Psychosocial variables such as better perceived quality of life (Balazard et al., 2023; Kaur et al., 2021), including physical, emotional, cognitive, social, and role functioning (Balazard et al., 2023), were positively associated with adherence. Additionally, factors such as patients' understanding of their medication regimen, their attitudes towards treatment, and self-efficacy in medication management emerged as relevant predictors of adherence behaviour (Kaur et al., 2021).

In the sociodemographic sphere, age was the most consistently reported variable. Non-adherence was more frequent among both younger patients (under 50) (Kuo et al., 2022; Rinder et al., 2024) and older individuals (over 65 or 70) (Kuo et al., 2022; Rinder et al., 2024; Yerrapragada et al., 2021). Other contributors to non-adherence included lower income (Rinder et al., 2024), being a surviving spouse, and receiving care in certain geographic regions (Yerrapragada et al., 2021).

Intervention supporting medication adherence

Among the studies reviewed, only one investigated the implementation of a dedicated intervention designed to enhance adherence to oral therapies in BC patients (Chaix et al., 2019). This study introduced an ML-powered chatbot that delivered personalised information via text and offered support for treatment management. Overall, the chatbot was well received: patients reported high levels of satisfaction (93.95%) and demonstrated frequent engagement with the tool. One of its features was a medication reminder system, which users could activate autonomously. Despite the study's large sample (n = 958), only a small subset of participants (n = 33; 3.44%) used the reminder function consistently enough to allow for the evaluation of its impact on adherence. Among these patients, a statistically significant improvement in adherence was observed, with compliance increasing by 20% (p = 0.04).

Risk of bias

Table 7 provides a summary of the risk of bias and applicability assessments.

Table 7. *Risk of bias assessment – Prediction Model Risk of Bias Assessment Tool (PROBAST)*

First author, year					Applicability concerns			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Balazard, 2023	Low	Low	Low	High	Low	Low	Low	High	Low
Kaur, 2021	Unclear	Unclear	Low	High	Low	Unclear	Low	High	Low
Kuo, 2022	Low	High	Low	High	Low	Low	Low	High	Low
Masiero, 2023	Low	Unclear	Unclear	High	Low	Low	High	High	High
Rinder, 2024	Low	Low	Low	High	Low	Low	Low	High	Low
Yerrapragada, 2021	Low	Low	Low	High	Low	Low	Low	High	Low

RoB = risk of bias.

All studies describing ML-based predictive models were rated as having a high overall risk of bias according to the PROBAST tool (Moons et al., 2019). As previously discussed in the context of Study 2, under PROBAST guidelines, a high risk in any single domain leads to an overall high-risk classification. In this case as well, the elevated overall risk primarily arose from issues within the analysis domain, which assesses the adequacy of statistical methods and analytical procedures. Notably, none of the included studies fulfilled the key requirements for thoroughly assessing model performance. In particular, they failed to report calibration analyses—such as calibration plots or statistics like the Hosmer-Lemeshow test – despite these being essential to evaluate how closely predicted risks align with observed outcomes. While many studies included discrimination metrics, such as AUC values, PROBAST emphasises that both discrimination and calibration are necessary for a robust evaluation of predictive models. Without proper calibration, predicted probabilities may be misleading and compromise their clinical utility, potentially resulting in suboptimal decision-making (Alba et al., 2017; Moons et al., 2019).

The only study among those analysed in Study 2 that was assessed as having a high risk of bias within the predictors domain (Kuo et al., 2022), was also included in the present systematic review. This domain specifically evaluates the selection and measurement of predictors and their potential to introduce bias. As discussed in section xxx, the authors identified the duration of therapy discontinuation and duration of medication use as the most influential predictors in their model. However, these variables are inherently unavailable at treatment initiation, which limits the model's applicability at that stage. Using post-treatment variables for early prediction undermines the model's prospective utility and raises important methodological concerns.

In addition, one study raised concerns regarding applicability. It is important to clarify that the applicability domain in the PROBAST framework does not assess the general applicability of a model but instead examines its alignment with the predefined focus of the review (Moons et al., 2019). In this case, the assessment was guided by the specific review question addressing ML models developed to predict adherence to oral therapies in BC patients. The models by Masiero et al. were flagged for concerns in the outcome domain, as they do not directly predict adherence. Instead, they target outcomes considered to be associated with adherence, namely, (1) short- and long-term adverse effects and (2) patients' physical condition and comorbidities (Masiero et al., 2023). This indirect approach limits their relevance to the central review objective.

Lastly, it should be noted that several items, and, consequently, their respective domains, were rated as "unclear" due to insufficient reporting of critical methodological details across studies.

The only study identified that described an intervention to improve medication adherence (Chaix et al., 2019) was assessed using the methodological quality scale developed by Downs and Black (Downs & Black, 1998), as the PROBAST tool is not suitable for studies that do not involve the development or validation of predictive models. As detailed in Table 8, the study showed consistently low scores across all areas of evaluation, suggesting a substantial risk of bias. The "reporting" section was particularly weak (score: 5/11), mainly due to limited information on participants characteristics, the distribution of confounding variables, and unclear reporting of some results. The lack of essential demographic and clinical data also affected the external validity score (0/3), as the relevant items could not be adequately assessed. Internal validity (3/7) was compromised by the unblinded nature of the intervention and the low level of engagement with the reminder system observed in participants. A further source of concern was the risk of selection bias (score: 1/6), largely due to the absence of random allocation and the overall poor description of the sample and confounders. Finally, the analysis related to adherence lacked statistical power (score: 0/5), as only a small fraction of participants engaged with the intervention long enough to allow meaningful adherence evaluation.

Table 8. *Risk of bias assessment – Downs & Black's Methodological Quality Scale*

First author, year	RB (0-11)	EV (0-3)	IV (0-7)	SB (0-6)	P (0-5)	Tot (0-32)
Chaix, 2019	5	0	3	1	0	9

RB = reporting bias; EV = external validity; IV = internal validity; SB = selection bias; P = power; SD = standard deviation.

3.3.4 Discussion

This systematic review maps the emerging field of AI applications targeting medication adherence in BC care, shedding light on current approaches and future directions.

The limited number of eligible studies (*n* = 7), all published between 2019 and 2024, indicates that the integration of AI into this domain is still at an early stage. Nevertheless, the available evidence indicates that ML models may become valuable tools for identifying patients at risk of non-adherence and for capturing patterns in medication-taking behaviours with increasing sophistication (Kaur et al., 2021; Kuo et al., 2022; Rinder et al., 2024; Yerrapragada et al., 2021). At the same time, the review highlights a series of persistent methodological and practical limitations that currently hinder the full implementation of these technologies, underscoring the importance of advancing research in this area.

Predictive models

We will begin by examining the key insights derived from studies developing ML-based predictive models. With the exception of the study by Rinder et al., which drew upon a large dataset of 229,695 individuals (Rinder et al., 2024), most of the included studies relied on sample sizes comparable to those typically found in research using conventional statistical techniques. This observation suggests that the distinctive advantage of AI, namely, its capacity to manage and learn from vast amounts of data, remains largely underexploited in this area. Harnessing larger, high-quality datasets could improve both the predictive accuracy and generalisability of these models (Riley et al., 2020; Tsegaye et al., 2025). One plausible explanation for the relatively modest sample sizes lies in the ongoing trade-off between quantity and relevance of data. Indeed, even a model trained on a massive dataset may yield results of limited clinical value if the data lack pertinent variables. For example, the study by Rinder et al. failed to include any psychological or psychosocial measures (Rinder et al., 2024), despite consistent evidence showing that such factors (e.g., depression, beliefs about treatment) are associated with non-adherence (Gast & Mathes, 2019; Horne et al., 2013). A similar issue emerges in smaller datasets, including those used in the studies analysed in Study 2. Among these, only three studies included psychosocial variables, and two of them adopted a prospective design (Shinn et al., 2022; Yanez et al., 2021). Only one study using a larger retrospective cohort (Meneveau et al., 2020) included psychological variables, specifically the presence of depression and anxiety. However, even in this case, more fine-grained constructs, such as treatment beliefs, were missing. A comparable pattern is evident in the predictive models examined in the present systematic review. Only half of these included psychosocial variables as candidate predictors (Balazard et al., 2023; Kaur et al., 2021; Yerrapragada et al., 2021). Among them, Kaur et al. considered specific psychological constructs such as medication attitudes, medication self-efficacy, and knowledge about BC survivorship, but relied on a very small cohort of just 32 participants (Kaur et al., 2021). Similarly to Meneveau et al., Yerrapragada et al. used a retrospective cohort that contained only a limited psychological indicator, namely, the presence of neurotic disorders (Yerrapragada et al., 2021). The only partial exception observations is Balazard et al., who analysed the large CANTO cohort that includes several psychological dimensions, such as quality of life, self-reported depressive symptoms and anxiety, and future perspectives (Balazard et al., 2023). Taken together, these observations highlight one of the main limitations of using large databases to develop adherence predictive models: although extensive, such datasets often lack many of the most relevant determinants of non-adherence, particularly psychosocial constructs such as medication beliefs, which are typically not collected in routine clinical practice.

Additionally, many of the predictors identified in these ML-based models, such as side effects, treatment complexity, and patient age, are consistent with findings from previous studies using traditional statistical analyses or qualitative approaches (Given et al., 2011; Nizet et al., 2022; Pezzolato, Spada, et al., 2023; Yussof et al., 2022). This alignment is not unexpected. The strength of AI does not primarily reside in identifying entirely new predictors, but rather in its ability to detect complex patterns, model intricate relationships between variables, and improve predictive performance through more nuanced data interpretation.

While a variety of metrics, such as accuracy, sensitivity, specificity, AUC, and the concordance index, have been employed to evaluate the predictive performance of AI models, these metrics alone do not offer a complete picture of model reliability or clinical value. Performance indicators must be interpreted in light of additional considerations to assess whether the predictions are not only statistically sound but also meaningful in real-world clinical settings (Seneviratne et al., 2020; N. H. Shah et al., 2019). For instance, two studies reported exceptionally high predictive accuracy despite relying on relatively small samples (n = 32 and n = 385, respectively) (Kaur et al., 2021; Kuo et al., 2022), a factor that may compromise the models' robustness and generalisability. Furthermore, a predictive model, no matter how accurate, has limited practical utility if it does not inform or trigger actionable clinical decisions or if its integration into healthcare systems is not feasible from a cost-benefit perspective (Seneviratne et al., 2020). These dimensions, clinical actionability and implementation feasibility, were largely overlooked in the included studies. Accordingly, the reported model performances should be interpreted with a degree of caution, acknowledging the gap between accuracy and real-world applicability.

All studies included in this review were judged to be at high overall risk of bias according to the PROBAST criteria. This assessment was primarily influenced by methodological shortcoming identified in the analysis domain. Although most studies reported discrimination metrics, indicating how effectively a model distinguishes between adherent and non-adherent patients, none provided a calibration assessment, which raises important concerns about the reliability of predicted probabilities (Moons et al., 2019). Discrimination alone offers only a partial evaluation of model performance. Calibration, on the other hand, measures the agreement between predicted risks and actual outcomes and is essential for determining the trustworthiness of probability estimates produced by the model. For instance, a model that lacks adequate calibration may systematically overpredict or underpredict adherence risk, potentially leading to inappropriate clinical decisions, such as over-intervening in low-risk patients or failing to support those at higher risk (Alba et al.,

2017). This omission constitutes a critical limitation, as calibration is necessary for ensuring that predictive tools are not only statistically accurate but also clinically meaningful. The underreporting of calibration is not unique to this field. For example, a large-scale review of cardiovascular disease prediction models found that only 36% (259 out of 717) included any calibration analysis (Wessler et al., 2015), suggesting a broader issue in predictive modelling research.

Another recurring methodological weakness was the absence of external validation, which compromises the generalisability of findings across different clinical contexts. Although three studies reported some form of internal validation, using approaches such as cross-validation or partitioned datasets (Balazard et al., 2023; Rinder et al., 2024; Yerrapragada et al., 2021), none assessed their models on fully independent external datasets. This finding is consistent with the trend already noted in Study 2, where no study reported external validation and only two reported internal validation. External validation is crucial for determining whether a model retains acceptable performance when applied to new patient populations with potentially different characteristics, care pathways, or data sources. This step becomes particularly important when model are trained on limited or non-representative samples (G. S. Collins et al., 2024), as was the case for several studies included in this review. According to the recommendations by Collins and colleagues, the entirety of available data should be leveraged during model development, supported by robust internal validation techniques, while external validation should be conducted in subsequent phases of research (G. S. Collins et al., 2024). Although no external validation studies were identified for the predictive models reviewed here, it remains possible that such investigations are currently underway or forthcoming.

An additional critical issue emerging from the studies on predictive models is the complete absence of information regarding their clinical implementation. None of the included studies reported attempt to integrate the developed models into routine practice, underscoring a persistent disconnection between algorithm development and its practical application in real-world healthcare settings. This lack of translation from research to practice reflects a broader and well-documented challenge in the field of ML in healthcare, commonly referred to as the above mentioned “implementation gap” (Chen & Asch, 2017; Seneviratne et al., 2020). Despite increasing enthusiasm surrounding AI technologies, their actual uptake in clinical environments remains limited, often due to factors such as insufficient evidence of clinical utility, lack of cost-effectiveness evaluations, integration difficulties with existing workflows, and concerns about accountability or transparency. These issues will be examined in greater detail in the *Clinical implications* section.

In conclusion, the predictive model studies reviewed here exhibit a range of methodological shortcomings, most notably, the absence of external validation, neglect of calibration assessment, and failure to address implementation. These limitations undermine both the credibility and clinical usefulness of the proposed models. To ensure that AI-based approaches genuinely contribute to improving adherence monitoring and intervention, future research must prioritise methodological rigour alongside clear pathways for clinical translation and integration.

AI-powered interventions

This systematic review was designed not only to investigate how AI technologies are being used to predict medication adherence among BC patients, but also to explore their potential role in actively supporting adherence. Strikingly, only one study describing an AI-based intervention aimed at promoting adherence was identified (Chaix et al., 2019). This alone is a meaningful finding, suggesting that the application of AI for direct support in this context remains largely unexplored and may represent a promising area for future research.

Closer examination of the included intervention study yields several insights. While the chatbot developed by the authors was not exclusively focused on adherence support, the results indicated some beneficial effects in this area, implying that AI-powered conversational agents may hold potential for engaging patients and enhancing medication-taking behaviours. Nevertheless, the evidence remains preliminary and should be interpreted with caution. In particular, only a small proportion of participants (33 out of 958, or 3.44%) made sufficient use of the reminder feature to allow assessment of its impact on adherence. This low engagement rate raises critical concerns about the real-world feasibility and effectiveness of this tool in fostering sustained behavioural change. Additionally, the methodological weaknesses highlighted in the risk of bias assessment, especially those related to incomplete reporting of participant characteristics, potential confounding variables, and the reporting of the study's findings, further limit the interpretability of the results. To strengthen the evidence base, future studies should aim for more rigorous designs, ideally incorporating a control group and clearly defined adherence outcomes. Moreover, a greater emphasis on evaluating patient engagement and usage patterns will be essential to understand how and for whom AI-based tools can be most effective in supporting adherence.

An additional consideration of particular relevance concerns the safety of the AI tool. In the study reviewed, the chatbot was not limited to supporting medication adherence; it also functioned as an informational resource, responding to patients questions. This dual role demands a high degree of reliability, as any dissemination of

inaccurate or misleading content could pose serious health risks. In this regard, it is noteworthy that the same chatbot was subjected to rigorous testing in a blinded, randomised controlled noninferiority trial aimed at comparing the quality of the information it provided with that delivered by physicians. The results demonstrated that, in terms of informational accuracy and quality, the chatbot performed at a level comparable to that of physicians (Bibault et al., 2019).

Another point worth noting is that the functions performed by the AI-driven chatbot in the study described here—namely, providing patients with reliable information and offering personalised reminders—can in fact be effectively implemented without relying on AI technologies. For instance, the multi-component intervention piloted in Study 5 of this thesis delivered reliable information through a webpage and sent personalised reminders via a WhatsApp extension. The characteristics of this intervention, together with its feasibility and perceived usefulness, are presented in detail in Chapter 4.

Ethical and safety considerations

Guaranteeing the safety of AI technologies is a critical concern, both in their clinical implementation and in the deployment of predictive models (Seneviratne et al., 2020). However, the scarcity of real-world implementation studies makes it difficult to assess the potential risks and unintended consequences associated with their use. Drawing a parallel with pharmaceutical development, the integration of AI-based tools into clinical practice should involve early and sustained engagement with regulatory authorities. For instance, the US Food and Drug Administration has already introduced guidelines for evaluating the performance of medical devices that incorporate AI and ML components (U.S. Food and Drug Administration, 2017). Importantly, regulation should not be viewed as a one-time requirement, but rather as an ongoing process requiring continuous oversight, post-deployment monitoring, and surveillance mechanisms (Williamson & Prybutok, 2024; Yang et al., 2025).

The protection of patient privacy and data security is a fundamental concern when deploying AI technologies in healthcare, and is inextricably linked to the broader issue of safety. The reliance of ML models on large volumes of highly sensitive personal health information exposes them to significant cybersecurity risks, including data breaches and ransomware attacks, which may not only compromise individual confidentiality but also undermine public confidence in these technologies (Gawankar et al., 2024; Williamson & Prybutok, 2024). To address these vulnerabilities and promote ethical deployment, Gawankar et al. proposed a unified framework, termed the "Integrated Security and Ethics Model," that draws on multiple theoretical perspectives. Through a comprehensive literature review, the authors combined

elements from five frameworks: Information Privacy Theory, the HBM, the General Data Protection Regulation (GDPR) framework, the National Institute of Standards and Technology (NIST) Cybersecurity Framework, and the Technology Acceptance Model. The resulting model provides a structured approach to embedding ethical principles, such as fairness, transparency, accountability, and privacy, into the development and implementation of AI systems in clinical contexts. It is intended as a guiding resource for developers, clinicians, and policymakers working at the intersection of health and technology (Gawankar et al., 2024).

A further critical concern in the use of AI within healthcare is the risk of algorithmic bias, which must be proactively addressed. This type of bias arises when ML models, especially if trained on datasets that are not representative of the broader patient population, lead to unfair or discriminatory outcomes, particularly when applied to groups outside the scope of the original data or model design (Arigo et al., 2024; Panch et al., 2019). In response to these challenges, institutions such as the Agency for Healthcare Research and Quality and the National Institute for Minority Health and Health Disparities have issued a set of five core principles aimed at helping developers and stakeholders navigate and reduce bias across all phases of the algorithm lifecycle. These principles include: (1) promoting health and healthcare equity; (2) fostering transparency and explainability; (3) engaging patients and communities; (4) recognising algorithmic fairness-related trade-offs; and (5) instituting mechanisms of accountability for equity and fairness in AI-driven clinical outcomes (Arigo et al., 2024; Chin et al., 2023).

Another critical issue that warrants attention is transparency, which is emphasised in the second guiding principle proposed by the Agency for Healthcare Research and Quality and the National Institute for Minority Health and Health Disparities. Due to their complexity and opaque nature, ML models are often perceived as "black boxes," making it difficult for clinicians and stakeholders to understand how specific decision or outputs are reached. This opacity can undermine trust in AI-assisted decision-making, particularly in clinical contexts (Chin et al., 2023; Khan et al., 2024). To enhance model interpretability, some researchers have employed techniques like Shapley values, which attempt to clarify the influence of individual input variables on the model's predictions. Two studies in this review adopted this method (Kuo et al., 2022; Masiero et al., 2023). However, such tools offer only partial insights, as they are heuristic-based and do not provide a complete understanding of the model's internal logic. Notably, most of the studies included in this review did not utilise such interpretability approaches. Ongoing research aims to develop more robust and transparent techniques that can make the decision-making process of ML models more accessible and comprehensible (Khan et al., 2024).

To conclude, this section has examined the principal ethical and safety challenges posed by the expanding integration of AI into healthcare practice. It has also introduced several frameworks designed to guide the responsible development and deployment of these technologies, reflecting a growing awareness within the scientific community of the need to weigh innovation against potential harm. Realising the full promise of AI requires more than technical advancement, it demands a strong commitment to addressing ethical risks through consistence adherence to well-established principles and regulatory standards. Crucially, greater attention must be paid to the implementation stage, where the actual impact of AI tools in real-world clinical environments can be assessed. Embedding AI development within a cycle of ongoing evaluation, transparent reporting, and iterative improvement would help build trust in these technologies and ensure they serve the best interests of patients and HCPs alike.

Study limitations

This review is subject to several limitations that should be acknowledged. First, despite the use of a comprehensive and systematic search strategy, it remains possible that some relevant studies were not captured, particularly those published in languages other than English, which were excluded and may contain pertinent findings.

Second, the relatively recent publication dates of several included studies suggest that some follow-up work, such as external validation or implementation efforts, may still be in progress. The lack of such data at the time of review may limit the completeness of the current evaluation and underscores the need for ongoing monitoring as new evidence becomes available.

Third, the substantial heterogeneity observed across the included studies, particularly with respect to how adherence was measured, the variables selected, model performance metrics, research objectives, and sample sizes, poses challenges for cross-study comparison and synthesis. However, this variability also highlights the developmental nature of this research area and may offer valuable insights into emerging directions and methodological diversity.

An additional consideration is the potential influence of cancer stage on adherence behaviour. As stated in a previous section, individuals with early-stage BC may experience different psychological and motivational dynamics than those with advanced or metastatic disease, potentially affecting their engagement with treatment. This hypothesis will be further discussed in Chapter 4, were two original studies will focus on mBC patients experiences and perspectives on medication adherence. For what concerns this review, the inclusion of a mixed BC population

(encompassing both early and late-stage cases) may limit the generalisability of findings across specific subgroups.
Finally, given the rapid pace of technological advancement in AI and ML, the conclusions drawn from this review may quickly become outdated. As new studies are continuously being published and AI capabilities evolve, future updates will be essential to maintain the relevance and accuracy of the evidence base.

Clinical implications
A number of important clinical implications emerge from the analysis of the included studies, with implementation challenges standing out as a recurring and central issue.
For predictive models to meaningfully impact patient care, their integration into routine clinical workflows is essential. Only by embedding these tools into day-to-day practice can HCPs reliably identify patients at risk of non-adherence and intervene early with personalised support strategies.

One key step toward bridging the gap between development and implementation involves shifting the focus beyond traditional performance metrics, such as sensitivity, specificity, or AUC, which, while useful for assessing predictive accuracy, do not necessarily capture a model's relevance or effectiveness in real-world settings. High scores on these indicators do not automatically translate into clinical benefit (Seneviratne et al., 2020; N. H. Shah et al., 2019). To address this, Seneviratne et al. propose evaluating predictive models through three critical dimensions: actionability, safety, and utility (Seneviratne et al., 2020). *Actionability* refers to the capacity of a model to inform a concrete response by HCPs or patients. For example, a model embedded within an electronic health record system could generate alerts for clinicians when a patient is identified as being at high risk for non-adherence. These alerts could then trigger specific interventions, such as tailored counselling, targeted education, or referral to adherence-enhancing digital tools. *Safety*, previously discussed in detail (see *Ethical and safety considerations*), remains a foundational requirement, ensuring that predictive models do not produce harmful consequences or mislead clinicians. *Utility* focuses on the model's real-world impact in terms of cost-effectiveness and clinical benefit. Key questions include: does the model improve adherence outcomes? Does it reduce the financial burden associated with non-adherence? Is its use sustainable within current healthcare systems? These considerations must guide both the initial development and the subsequent evaluation of AI-based tools. Proactively addressing them can help ensure that predictive models not only perform well in theory but also deliver measurable value in practice.

Beyond directly addressing the shortcomings identified through this systematic review, an alternative approach to the same challenge for which predictive models may represent a solution—namely, how to allocate limited healthcare resources more effectively—may involve the use of simple screening tools and the routine training of HCPs to administer them. A notable example is the brief screener *Making Medicines Work For You* (©MMWFY), developed to foster open and non-judgemental conversations on medication use between HCPs and patients (Weinman et al., 2019). This approach, and its exemplary implementation, are described in greater detail in Chapter 5.

In relation to AI-powered chatbots, further investigation is warranted to better understand their potential in enhancing medication adherence. As outlined in the ethical and safety considerations, concerns such as data privacy and the interpretability of AI systems remain highly relevant to these tools (Basharat & Shahid, 2024; May & Denecke, 2022). Provided these fundamental safeguards are respected, recent advancements in AI offer promising opportunities to create digital solutions that support patients throughout their cancer care. For example, AI-driven systems could help individuals monitor their adherence, provide timely reminders, and assist with managing side effects associated with treatment. Additionally, chatbots trained using validated clinical guidelines and evidence-based content may offer immediate, accessible guidance and information to patients, potentially alleviating some of the demand on HCPs (Chaix et al., 2019; Xu et al., 2021). Nevertheless, to ensure these technologies are both effective and widely adopted, coordinated efforts among researchers, developers, clinicians, and policymakers are essential in driving their responsible design, implementation, and integration into routine care.

Conclusions

This systematic review offers a detailed and up-to-date examination of how AI is currently being applied to predict and support medication adherence in patients with BC.

The findings suggest that AI technologies have considerable potential to enhance the detection of non-adherence, support the monitoring of patient behaviour, and enable timely interventions. Nonetheless, several obstacles still need to be overcome before these tools can be seamlessly integrated into routine clinical care.

Greater attention is needed in the implementation phase, which is often neglected in existing studies, as well as in designing approaches that actively engage patients. To ensure that AI-driven solutions are both effective and trustworthy, their development

and deployment must be guided by ethical principles and supported by thoughtful, rigorous planning across all stages, from initial design to real-world use.

4. Adherence and metastatic breast cancer

A comprehensive overview of the scientific literature on non-adherence among BC patients was provided in the previous chapter. In particular, the discussed reviews examined adherence-supporting interventions specifically designed for this clinical population (Pezzolato, Marzorati, et al., 2023) and predictive models developed to identify determinants of non-adherence, with the aim of facilitating the identification of high-risk patients for targeted interventions (Pezzolato, Spada, et al., 2023).

Conversely, the present chapter presents two original studies involving the direct participation of mBC patients recruited at the European Institute of Oncology (IEO) in Milan, Italy. The decision to narrow the focus of these investigations to individuals with metastatic disease stems from two main, closely interconnected considerations. First of all, the previously described reviews have confirmed a significant disparity in the amount of research conducted on mBC when compared with early-stage disease (Pezzolato, Marzorati, et al., 2023), reflecting a well-documented trend (Hooper J. et al., 2024; Thrift-Perry et al., 2018). Secondly (possibly as a result of the above), as already highlighted in Chapter 1, the literature presents conflicting and inconclusive findings regarding non-adherence in this clinical population: while some studies have reported adequate adherence rates among mBC patients (Conley et al., 2022; Komatsu et al., 2020), others have found suboptimal levels comparable to those observed in early-stage BC (Delea et al., 2014; Husinka et al., 2021; Yerrapragada et al., 2021). Accordingly, the following two studies form part of a broader effort to deepen the understanding of non-adherence in mBC and to help address the previously identified gap in the literature, by adopting both a qualitative (Study 4) and a quantitative approach (Study 5).

4.1 Study 4: Metastatic breast cancer patients experiences with oral treatments in their own words: the focus groups

The study presented in this section is part of a two-year research project funded by Pfizer, titled *Enhancing Therapy Adherence Among Metastatic Breast Cancer Patients*. The project comprised three complementary studies, all focused on the issue of medication non-adherence in individuals living with mBC: a retrospective study, a qualitative study, and a randomised controlled study. Before turning to the qualitative study, a brief overview of the other two studies is provided.

Within the retrospective study, two predictive algorithms were developed in collaboration with a data science company, using NLP and ML techniques applied to sociodemographic and clinical data already available in IEO's electronic health records

(Masiero et al., 2023). These models estimate the likelihood of patients experiencing certain conditions associated with lower adherence (i.e., "physical status and comorbid conditions" and "short- and long-term side effects") thus providing an indirect prediction of the risk of non-adherence. This study aligns with the scope of one of the systematic reviews discussed in Chapter 3 (Study 3), in which it has been analysed and further examined.

The randomised controlled study was conducted to assess the effectiveness of a decision support system (Masiero et al., 2023) in the form of an educational web-page, which provided information about mBC, medication adherence, and practical strategies to support patients in adhering to their prescribed treatments. The educational material, first embedded in the decision support system, was subsequently tested in the factorial pilot optimisation study described later (Study 5). In parallel, a range of sociodemographic, clinical and psychological variables was collected during the trial and used to refine the predictive models developed in the retrospective study, enabling the integration of psychological variables that were not available in the original training dataset.

In the context of this doctoral thesis, the qualitative study (Masiero et al., 2024) is particularly relevant and will therefore be discussed in detail in the present section. It provides a natural link between the broad-scope reviews presented in Chapter 3, which included BC patients across all disease stages but were predominantly focused on early-stage cases, and the subsequent Study 5, where a multi-component intervention for mBC patients is pilot tested.

Given the limited attention devoted to the barriers and facilitators of adherence among patients with mBC, especially when compared to the extensive focus on early-stage disease, it becomes essential to explore the factors that influence medication-taking behaviour in this population. At the same time, the increasing presence of digital tools in healthcare underscores the importance of investigating patients' perspectives on the role of eHealth in supporting their therapeutic journey. Are such tools perceived as useful? Would patients be inclined to use them for self-management? Would they trust them? And what features would they expect or value most?

To address these questions, a series of four focus groups was conducted involving individuals living with mBC. These group discussions provided a space for participants to speak openly with one another, exchange personal experiences, and reflect on shared challenges and strategies. Focus groups were preferred over individual interviews because of their potential to generate a dynamic discussion capable of eliciting themes and meanings that might otherwise have remained hidden in one-to-one settings. More specifically, we anticipated that most participants would be

adherent to their medication while at least a few would not. By bringing together patients with different medication experiences, we expected that an open group conversation would yield a richer and more nuanced understanding of the topic. It was also assumed that discussing with peers facing similar situations would make participants more inclined to share personal views and experiences than in an individual interview, where they would interact solely with the researcher.

The analysis of the material collected through these sessions provides valuable insights into the lived experiences of mBC patients, as expressed in their own words, as well as into their expectations regarding electronic tools that may support them throughout their cancer care journey.

4.1.1 Aims of the study

This qualitative study investigated a range of individual and contextual factors influencing adherence to oral anticancer therapies among patients with mBC, alongside the potential role of eHealth technologies in supporting treatment adherence. The research aimed to explore patients' representations of their illness and treatments, perceived barriers and facilitators to adherence, and attitudes towards digital tools designed to assist them throughout the therapeutic journey.

The objective was to gather insights that could inform the development of technologies that are responsive to patients' needs. To achieve this, the study adopted an exploratory approach, aiming to uncover central themes and patterns emerging from patients' direct accounts of their experiences of living with mBC and managing its treatments.

4.1.2 Material and methods

Study design

This research employed a qualitative approach to investigate the experiences and perspectives of individuals diagnosed with mBC in relation to treatment adherence and the potential integration of digital health technologies into clinical care. Data were collected through a series of four focus groups, which facilitated open discussion among participants on topics such as the management of oral anticancer therapies, informational needs, and perceptions of both barriers and facilitators to adherence.

The collected transcripts were analysed using network analysis and sentiment analysis, with the goal of mapping conceptual associations and identifying emotional tones embedded in patients' narratives. This analytical approach enabled a structured interpretation of the connections among key themes and the affective dimensions underlying patients discourse.

The study was approved by the Institutional Review Board of IEO in June 2022 (R1508/21-IEO 1594). All participants gave their informed consent, and procedures were conducted in line with the ethical principles outlined in the Declaration of Helsinki.

Inclusion and exclusion criteria

To take part in the study, individuals had to meet the following requirements: be at least 18 years old, have a confirmed diagnosis of mBC, be able to access the internet via a computer or tablet, and provide informed written consent. Exclusion criteria included the presence of psychiatric or neurological diagnosis, or any major medical condition not related to mBC.

Participants and recruitment

Nineteen women living with mBC and currently receiving treatment were included in the study. They were recruited using a convenience sampling approach, following referral by a breast oncologist at IEO. Each potential participant was subsequently approached by the psychologist responsible for the research, who explained the study objectives and procedures and obtained informed consent.

Procedure

The focus groups were organised in accordance with recognised standards for qualitative research (Krueger, 2014). Each session was facilitated by a team of three psychologists: one assumed the role of primary moderator, while the others supported the discussion as co-moderators, contributing to a collaborative and non-hierarchical atmosphere. The total sample of 19 participants was distributed across four distinct groups, each comprising four to five members. To support concentration and minimise participant fatigue, discussions were limited to 60-90 minutes and continued until thematic saturation was achieved.

In order to maximise inclusivity and logistical feasibility, all sessions were conducted remotely using the Zoom platform. Audio recordings were made of each discussion and subsequently transcribed verbatim by the research team. A semi-structured discussion guide was employed to steer the conversation, featuring open-ended questions grounded in prior literature and refined through input from a multidisciplinary panel of experts. The full discussion guide is provided in Appendix 3. Thematic redundancy was used as the criterion for concluding data collection.

Data analysis

Basic descriptive statistics were used to profile the sample. The qualitative material was independently coded by three research assistants and then reviewed by the senior researcher. Discrepancies were resolved through iterative discussions. As new codes emerged, earlier transcripts were revisited and recoded accordingly to ensure consistency. The thematic framework was developed inductively, grounded in participants' narratives.

To facilitate organisation and comparison, the data from each focus group were compiled into structured tables that included patient ID, verbatim statements, key terms, categories, subthemes, and overarching themes, each associated with a specific colour code. The transcripts were reviewed multiple times to ensure accurate classification. Keywords were extracted from the statements and inserted into the tables to support further stages of analysis. A second analyst cross-checked these keywords to ensure they adequately captured the meaning of the original responses.

The next analyses were conducted by the team of data scientists collaborating on the project (i.e., *Enhancing Therapy Adherence Among Metastatic Breast Cancer Patients)* and was carried out in two ways: first, by integrating all transcripts; second, by examining content within each of the four principal thematic areas. Textual data were preprocessed (cleaning, lemmatisation, tokenisation), and network analysis was then applied to map semantic connections between keywords, themes, and categories. This process enabled visualisation of how topic clustered and how different concepts were interrelated, revealing both the strength and directionality of these links. Additional network graphs mapped relationships between participants and categories, as well as between individuals and specific thematic constructs.

Sentiment analysis was also carried out using NLP techniques, relying on spaCy, an open-source library, for text processing. The emotional tone of sentences was classified using the FeelIT Python library, which had been trained on an Italian-language dataset. This tool assigned one of four emotional labels (joy, sadness, anger, or fear) based on the content. The underlying model was UmBERTo, a BERT-based architecture fine-tuned for Italian.

To visualise the emotional distribution across themes and participants, Circos plots were generated, offering a comprehensive overview of how specific emotional states were associated with different categories and individuals. These visualisations allowed for intuitive identification of emotional patterns within each thematic area. Finally, word clouds were created for each main theme and for the full dataset to highlight the most frequently used terms, offering an additional layer of insight into salient topics discussed across the groups.

4.1.3 Results

Descriptive analysis

A total of 19 women diagnosed with mBC (mean age = 55.95 years, SD = 6.87, range 46–70) took part in the study. Participants presented with various metastasis localisations (see Table 9). Regarding family history, 42.1% (*n* = 8) reported no familial occurrence of BC, 52.6% (*n* = 10) had first-degree relatives affected, and one participant (5.3%) had a second-degree relative with the disease.

Table 9. *Details of metastasis, surgery, and oral treatments among participants.*

Variable	Level	Overall (*N* = 19)
Age at eligibility, mean (min-max)		55.95 (46-70)
Metastatic localisation, *n* (%)	Bone	4 (21.1)
	Bone and lymph node	1 (5.3)
	Liver	1 (5.3)
	Liver and bone	2 (10.5)
	Lung	3 (15.8)
	Lung, bone, and lymph node	1 (5.3)
	Lung and liver	1 (5.3)
	Lung and pleural	1 (5.3)
	Lymph node	1 (5.3)
	Pleural	3 (15.8)
	Skin	1 (5.3)
Surgery, *n* (%)	Bilateral mastectomy	2 (10.5)
	Mastectomy left breast	6 (31.6)
	Mastectomy right breast	4 (21.1)
	Radicalisation	1 (5.3)
	Quadrantectomy left breast	3 (15.8)
	Quadrantectomy right breast	1 (5.3)
	No	2 (10.5)
Type of current oral therapy, *n* (%)	Oral chemotherapy	4 (21.1)
	ET	1 (5.3)

Variable	Level	Overall (*N* = 19)
	ET + targeted therapy	5 (26.3)
	Targeted therapy	9 (47.4)

ET = endocrine therapy.

Barriers, challenges, and supportive factors related to adherence

The thematic analysis of focus group discussions led to the identification of four overarching themes: (1) the personal clinical experience and care trajectory; (2) barriers encountered in maintaining adherence to oral anticancer therapies; (3) resources that supported treatment adherence; and (4) patients' views and attitudes toward digital technologies designed to promote adherence (see Table 10 for the list of themes, sub-themes, and illustrative quotes).

Table 10. *List of themes, sub-themes, and illustrative quotes derived from the qualitative analysis.*

Theme	Sub-themes	Illustrative quotes
Personal clinical experience	Clinical path, side effects, lifestyle, shared decision-making, dose adjustments, treatment management, HCP's support, trust, gratitude.	"Me too, like… let's say… my colleagues [t.n., laughs], I'm on an oral therapy, uh… for a couple of years now. Uh… I'm on an oral therapy that, basically, at the moment requires check-ups every 21 days and then, based on the results of those exams, uh… let's say, whether or not I take the 21-day therapy cycle. Mine is a metastatic BC with a bone metastasis, and for the moment, let's say, everything is under control."
Barriers	Side effects, going to the hospital, clinical values, negative lifestyle, patient-physician relationship, psycho-emotional distress, lack of perseverance, misunderstanding, other issues.	"It was a moment when… mm… the previous one I was taking was giving me problems, and so I wanted to stop it and I didn't know who… who to turn to. And… honestly, and again, it's probably just my personality, I became really discouraged and I wanted to give everything up, like, whatever… I mean, I would have stopped the pill I was taking."
Resources	Remote consultations, patient-physician relationship, well-being, nutrition, physical activity, positive lifestyle, treatment adjustment, support, medical checks, side effects re-evaluation, coping strategies related to medical intake, cancer-related coping strategies, positive treatment management, information.	"And there are moments when… when, life kind of… puts you to the test for other reasons, besides this, and so you tend maybe not to be always, uh... vigilant, you know. This thing, in my opinion… it's why I was saying that it's important for me to have a regular appointment with the doctor. [...] For me, this helps. Even if it's via video call, as I said […]. But for me, this appointment really helps, and this support that I know is there. And for me, it's essential."

Theme	Sub-themes	Illustrative quotes
Attitudes toward adherence-focused digital tools	Tailored tool, support/utility, patient-physician relationship, coping strategies, sense of community/social support, sharing positive experiences, information/educational content, reminder, doubts/scepticism.	"It's a bit, a territory where you have to be careful because, as we were saying, we're connected in a group of five and each one has a point of view, a sensitivity, a personal story. So trying to find a common tool that could work for everyone's problem isn't easy..."

BC = breast cancer; HCP = healthcare provider; t.n. = transcriber's note.

Word cloud analysis

The word cloud associated with Theme 1 (Personal clinical experience) revealed that terms most frequently mentioned by participants clustered around the sub-themes "clinical path" and "treatment side effects." These two areas appeared to dominate patients' narratives, underscoring their salience in the lived experience of mBC and oral therapies. Prominent words included key elements of the therapeutic trajectory, such as "therapy" (*n* = 16), "metastasis" (*n* = 6), specific medications like "ribociclib" (*n* = 6) and "letrozole" (*n* = 4), and procedures such as "surgery" (*n* = 4). By way of illustration, the word cloud for Theme 1 is shown in Figure 4, while those for Theme 2, 3, and 4 are presented in Appendix 4.

Figure 4. *Word cloud illustrating key terms associated with Theme 1: Personal clinical experience.*

Adapted from Masiero et al., Supportive Care in Cancer, 2024.

For Theme 2 (Barriers to adherence), the word cloud reflected the weight of physical and emotional challenges patients face. Words like "side effects" (*n* = 4), "stomachache" (*n* = 3), "problems" (*n* = 4), "lost hair" (*n* = 3) pointed to the disruptive nature of adverse effects on patients' motivation to follow treatment regimens. Additional terms such as "physicians" (*n* = 3) and "oncologist" (*n* = 2) emerged in the context of the therapeutic relationship, often linked to perceived difficulties in continuity of care or ineffective communication (see Appendix 4a).

In relation to Theme 3 (Resources supporting adherence), the most recurrent words indicated both professional and personal forms of support. Patients often cited

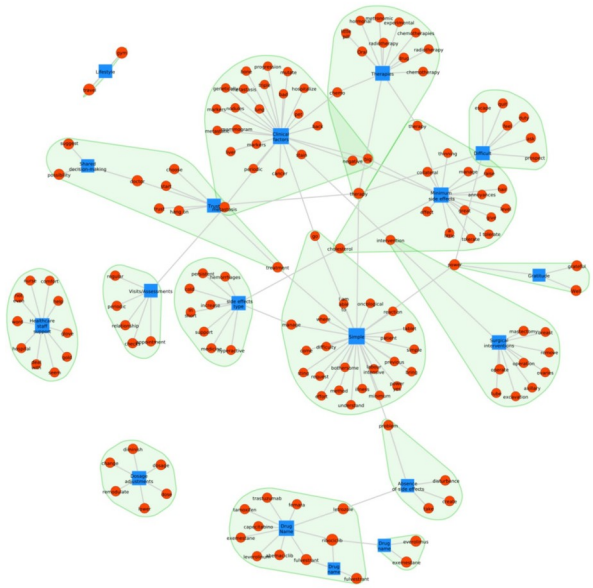
"physicians" (*n* = 6) and "psychologists" (*n* = 5), highlighting the central role of trusted HCPs in facilitating sustained adherence. Other frequent references included personal coping strategies such as "moving forward despite difficulties" or making lifestyle adjustments (e.g., "having a more active life" and "adopting healthy lifestyles"). The term "diet" (*n* = 5) also appeared repeatedly, reflecting the perceived benefits of nutrition in managing therapy side effects and sustaining physical well-being. Digital tools and remote healthcare services (e.g., mobile apps or teleconsultations) were mentioned as practical additions to conventional support systems (see Appendix 4b).

Finally, the word cloud for Theme 4 (Patients' attitudes toward adherence-focused digital tools) offered a snapshot of how new technologies are viewed in relation to treatment support. Common terms included "phone" (*n* = 3), "doctor" (*n* = 3), "person" (*n* = 3), and "support tool" (*n* = 2), along with action verbs such as "to know" (*n* = 3), "to find" (*n* = 3), and "to see" (*n* = 2). These entries suggest that patients valued technologies that improved access to information and fostered a sense of connection and social support with both HCPs and fellow patients (see Appendix 4c).

Network analysis

Within Theme 1, which explores patients' experiences with oral anticancer therapies, several key dimensions emerged as central nodes in the relational structure: clinical variables, treatments, perceived simplicity of management, levels of trust in therapy and HCPs, and the nature and intensity of side effects. These elements, corresponding to subthemes such as clinical pathway, treatment-related side effects, management strategies, and trust, emerged as distinct but interconnected semantic clusters. Among these, the subthemes "side effects," "ease of managing the treatment," and "trust in the therapy" were particularly central, suggesting their key role in shaping patients' adherence behaviours. The network analysis revealed clusters of pre-processed and tokenised keywords linked to each category, with some terms acting as bridges across multiple semantic areas. These overlapping connections underscore the complex interplay between physical, emotional, and cognitive dimensions of patients' lived experiences with oral anticancer therapies. By way of illustration, the network analysis of Theme 1 is shown in Figure 5, while those of Theme 2, 3, and 4 are presented in Appendix 5.

Figure 5. *Network analysis of Theme 1 (Personal clinical experience), illustrating the main concepts discussed and their interconnections.*



In the network map, blue squares represent the main categories, while red circles indicate the key words.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.

Within Theme 2, which focuses on the barriers to adherence to oral anticancer therapies, the most prominent category emerging from the network analysis was "psycho-emotional distress." This construct encompasses a range of emotional responses such as anxiety, stress, and depressive symptoms that were often linked to specific treatment-related factors. Contributing elements included frequent changes in the HCP responsible for the patient, the burden of side effects, psychological reactions, clinical outcomes, the logistics of hospital visits, limited understanding of the therapeutic plan, and perceived difficulties in patient-physician communication. These interconnected dimensions collectively formed a core cluster, underscoring how emotional distress can act as a powerful inhibitor of consistent adherence to prescribed treatment regimens (see Appendix 5a).

In contrast, Theme 3 centred on the resources and strategies that patients reported as helpful in maintaining adherence. Key facilitators identified in the network included coping mechanisms, such as adjusting the timing or dosage of medication. Another central category was "trust in the doctor," particularly when supported by continuity of care, clear and emphatic communication, and attention to managing side effects. This trust appeared to be reinforced by access to reliable information and personalised advice on dietary modifications. Although more peripheral in the network structure, elements like lifestyle adaptations, involvement in support groups, and access to remote care services (e.g., telemedicine) were also linked to enhanced adherence,

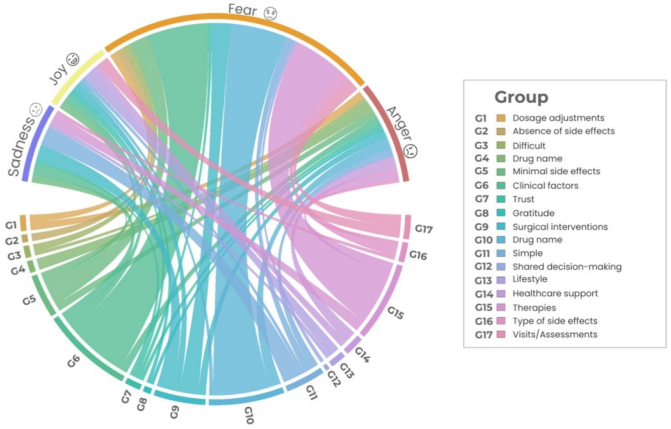
indicating their supportive role within a broader system of resources (see Appendix 5b).

Theme 4 explored patients' views on the use of technology to support adherence. The network analysis revealed the "sense of community and social support," referring to the sense of shared experience and support within peer communities, as the most central concept. Many participants saw virtual platforms, such as online support groups, as valuable spaces for exchanging practical advice, emotional encouragement, and reliable health information. These environments were described as fostering a sense of belonging and providing a meaningful supplement to clinical care. Nonetheless, ambivalence emerged around the effectiveness of technological tools: some patients expressed doubts about the utility or user-friendliness of such solutions in managing daily treatment routines. Interestingly, while coping strategies and patient-doctor communication were central in Theme 3, their marginal position in the network for Theme 4 suggests that patients may not yet perceive digital tools as effective means to activate or enhance these resources in the context of treatment adherence (see Appendix 5c).

Sentiment analysis

The emotional responses elicited by discussions on the experience of oral anticancer therapies revealed distinct affective patterns across thematic areas. Fear emerged as the most prevalent emotion, particularly in relation to references to the treatment process, medications, and personal clinical characteristics. Conversely, joy was the least commonly expressed emotion within Theme 1. When present, it was typically associated with feelings of reassurance regarding treatment simplicity or confidence in the prescribed therapeutic plan, two subthemes already identified as relevant in the network analysis. By way of illustration, the circos plot for Theme 1 is presented in Figure 6, while the corresponding plots for Theme 2, 3, and 4 are provided in Appendix 6.

Figure 6. *Circos plot for Theme 1 (personal clinical experience), illustrating the relationships between sub-themes and emotions.*
Adapted from Masiero et al., Supportive Care in Cancer, 2024.



In Theme 2, which explored perceived barriers to adherence, fear was again the dominant emotional tone, especially in connection to concerns about medical tests, adverse effects, and relational aspects of care. In particular, difficulties caused by frequent changes in the doctor in charge and poor communication appeared to generate emotional responses. In addition to fear, anger and sadness were frequently expressed when participants described specific side effects, highlighting how these symptoms emotionally affect patients and interfere with treatment engagement (see Appendix 6a).

By contrast, the emotional landscape changed considerably in Theme 3, which focused on facilitators promoting adherence. Here, joy and fear were expressed with comparable frequencies. Joy often surfaced in relation to narratives of psychological resilience and positive coping efforts. Notably, joyful expressions were particularly linked to the perceived human qualities of physicians, including empathy, availability, and continuity of care (see Appendix 6b).

With regard of Theme 4 (patients' perspectives on digital tools as potential support mechanism for adherence), joy once again predominated. This emotion was most frequently associated with the notion of shared experience and peer support, echoing the findings from network analysis, where the sense of community emerged as central. Participants valued opportunities to connect with others facing similar challenges and appreciated access to reliable information and educational content through technology. Interestingly, despite reservations and a degree of scepticism about the actual usefulness of digital platforms, these were not typically accompanied by negative emotional responses such as fear or sadness. However, certain categories that had previously been linked to positive emotions in Theme 3, such as coping strategies and communication with physicians, were not described with similar affective intensity in the context of technological tools. This might suggest that while patients recognise the potential value of digital resources, they may not yet perceive them as integral to the interpersonal or emotional dimensions of care that most strongly support adherence behaviours (see Appendix 6c).

4.1.4 Discussion

Our findings shed light on the multifaceted nature of adherence to oral anticancer therapies in the context of mBC disease, revealing an interplay of internal and external factors. These determinants are not limited to the clinical and pharmacological peculiarities of the disease and its treatment but also encompass psychological and relational dimensions, particularly those concerning interactions with HCPs. Additionally, the results offer preliminary insights into the characteristics that digital

health technologies should incorporate to effectively support both adherence and patients' psychological well-being.

The integration of word cloud and network analyses revealed two pivotal elements that influence adherence: the nature of treatment side effects and the quality of the patient-clinician relationship. Side effects were described as a considerable burden, impacting not only physical health but also psychological well-being and overall quality of life. These effects extended into daily functioning, interfering with employment, family responsibilities, and personal interests.

At the same time, the patient-clinician relationship emerged as a dual-edged factor. On the one hand, frequent changes in care providers and poor communication were seen as obstacles to maintaining adherence. On the other hand, when physicians were perceived as emotionally available and attentive to the patient's condition, they were identified as facilitators of adherence. Such relational qualities enabled more effective recognition and management of patients' needs and difficulties, thereby supporting a more engaged and consistent approach to treatment.

These relational dynamics also resonated with the sentiment analysis findings. Fear was a dominant emotion in relation to medical uncertainty, such as test outcomes or tumour markers, and also emerged in the context of unsatisfactory communication and discontinuity in care. Conversely, feelings of joy were more commonly expressed when patients spoke about the compassionate and human aspects of their relationship with clinicians. In contrast, the side effects were strongly associated with expressions of anger and sadness, reinforcing their role as a central barrier to adherence to treatment adherence.

Interestingly, these relational aspects are also difficult to quantify, which may help explain why none of the predictive models examined in Study 2 and 3 included predictors derived from them. Their omission could, at least in part, account for the limited predictive power reported in some models, where relevant but hard-to-collect variables were not available in the development datasets. This considerations also resonate with the findings of a meta-analysis of interventions to support adherence to endocrine therapy in BC (Finitsis et al., 2019), which suggested that approaches fostering bi-directional communication between patients and HCPs tended to be more effective. One possible interpretation is that such interventions may, even indirectly, engage these relational dimensions by promoting a sense of being listened to and involved in a meaningful relationship. A similar interpretation is reinforced by the findings of Study 5, described in the following sections, where many participants reported aspects of their interactions with the research staff (e.g., feeling listened to, reassured, supported, and involved in self-care) as the most valuable component of the intervention.

Moreover, some internal factors appeared to facilitate adherence, particularly the coping mechanisms patients employed in managing their condition. Among these, dietary adjustment, represented in the analysis by the keyword "diet," emerged as a relevant strategy. These adjustments were perceived as contributing both to treatment adherence and to patients' general physical well-being, potentially mitigating the adverse effects of the illness and its therapy. In addition, expressions of joy were frequently linked to patients' capacity to maintain constructive and adaptive thoughts about living with cancer on a day-to-day basis.

So far, the discussion has centred on the determinants most commonly raised by participants. To reflect the full range of the material generated during the focus groups, however, it is also important to include factors that emerged less frequently but were nonetheless perceived as meaningful by a subset of participants. In this regard, a system-level barrier was highlighted by three individuals across three different groups: they described the practical difficulty of travelling to the hospital on a regular basis to collect their medication and lamented the absence of more accessible options for obtaining refills. Although system-related determinants of adherence are recognised in the literature, they remain relatively underexplored (World Health Organization, 2003). A comprehensive, multidisciplinary strategy to improve adherence should therefore also take into account this dimension and aim to reduce structural obstacles that patients report in their treatment pathways.

A notable aspects of the findings concerns patients' views on the potential of eHealth technologies to support treatment adherence in clinical settings. Several participants pointed out that telemedicine could facilitate communication with HCPs, offering a platform to express concerns, discuss treatment-related challenges, and jointly develop coping strategies, particularly for managing side effects. Interestingly, while some degree of uncertainty and scepticism remained regarding digital tools, these technologies were not associated with emotions like fear or sadness. On the contrary, patients often expressed feelings of joy when discussing experiences such as engaging with peer support groups, exchanging personal stories, or accessing educational content through these platforms.

The analysis also underscores the value of combining human interaction, especially meaningful communication with HCPs, with technological resources such as digital support tools or mobile health apps. The frequent appearance of terms like "support tool," "phone," "doctor," and "person" within the thematic cluster suggests that successful eHealth interventions should not replace but rather complement traditional care practices. For instance, integrating risk prediction algorithms or digital decision aids into patient-provider consultations could enhance shared decision-making processes. Although existing research points to the potential of technology to improve

communication within the healthcare team, the use of such tools during oncology consultations remains underexplored (Yung et al., 2021).

Patients with mBC consistently emphasised how digital solutions might foster a greater sense of connection and peer support. Access to online communities composed of individuals facing similar challenges was regarded as a meaningful way to exchange insights and build emotional resilience. Recent studies have shown that many BC patients are open to integrating technology, such as internet-based resources, into their care routines. In this context, eHealth applications show promise in strengthening the patient-physician relationship, enhancing clinical communication, and potentially improving adherence to treatment regimens (Drewes et al., 2016). Ensuring a consistent focus on quality of life and long-term survival requires coordinated, personalised care, but this is something that conventional healthcare delivery models often fail to provide, particularly in complex cases such as mBC. Digital tools can address this gap by offering flexible, continuous, and tailored support. Evidence in the literature supports the feasibility and positive outcomes of remote interventions in this population, including digital resources aimed at improving patient-physician communication and delivering educational content (Qiu et al., 2021; Rincon et al., 2017).

Study limitations

While this study provides meaningful insights into the mechanisms underlying adherence to oral therapies in mBC, several limitations should be acknowledged. Firstly, although the decision to rely on focus groups rather than individual interviews was grounded in their ability to stimulate interaction and prompt the emergence of themes that might not surface in one-to-one conversations, this choice also carries certain drawbacks. Group discussions can intensify dynamics such as conformity and social desirability, potentially discouraging participants from sharing views they feared might be judged, dismissed, or considered unpopular by others or by the researchers. Given that medication adherence is a personal matter and can be associated with feelings of inadequacy or stigma, it is possible that some participants moderated their accounts or presented themselves in a more favourable light. To mitigate this risk, the focus groups were designed and facilitated to promote an open, respectful, and non-judgmental environment, helping participants feel safe to share their experiences.

Secondly, the use of a semi-structured discussion guide in focus groups, although beneficial for ensuring consistency across sessions and targeting specific clinical and psychological domains, may have inadvertently restricted the emergence of unexpected themes. A more open-ended approach might have allowed participants

greater freedom to introduce issues they perceived as personally significant, thereby reducing potential anchoring bias introduced by the researchers' framing of questions.

Moreover, the reliance on convenience sampling, combined with the single-centre origin of all participants, may have limited the representativeness of the sample and, consequently, the generalisability of the findings. In particular, recruiting through single-centre convenience sampling increases the likelihood that those who agreed to take part shared specific characteristics or motivations. As a result, certain perspectives may have been disproportionately represented in the data, while others, especially those held by individuals less inclined to participate, may have been insufficiently captured.

Another limitation lies in the exclusive reliance on patient self-report. The absence of perspectives from informal caregivers, who often have intimate knowledge of patients daily routines and emotional responses, may have led to an incomplete understanding of certain adherence-related dynamics, particularly those not consciously recognised or verbalised by patients themselves.

Finally, adopting a data-driven computational approach, combining word cloud visualisations, network analyses, and sentiment analysis, made it possible to highlight the recurrent terms, map co-occurrence patterns, and visualise sentiment tendencies. While these techniques offered an accessible and visually intuitive overview of the material, they remain limited in their ability to capture the depth, nuance, and contextual meaning embedded in narrative accounts. Quantitative representations of term frequency or co-occurrence do not necessarily reflect the emotional significance or personal meaning participants attribute to specific concepts. Importantly, all transcripts were first coded and interpreted by researchers who had also facilitated the focus groups, ensuring that the subsequent computational analyses were grounded in an in-depth, contextually informed understanding of the discussions. This sequential approach helps mitigate some of the limitations of computational text analyses, as the final interpretations remain aligned with the researchers' experiential and qualitative comprehension of the material. Even so, future research would benefit from integrating more nuanced qualitative methodologies capable of exploring both latent content and affective nuances in patients' discourse, which remain beyond the reach of current computational tools.

Conclusions

Given the significant impact of non-adherence on both survival outcomes and quality of life among patients with mBC, it is essential to prioritise early identification of the factors most likely to undermine sustained adherence to treatment. The findings from this study point to a constellation of interconnected determinants, ranging from

personal coping resources and relational dynamics with clinicians, to the physical and psychological burden of side effects, that should be taken into account when developing predictive models of non-adherence for use in clinical practice.

These models would benefit from embracing a biopsychosocial perspective, recognising that adherence is rarely influenced by isolated variables but rather by the interplay of emotional, cognitive, and contextual dimensions that evolve throughout the treatment trajectory.

In parallel, digital health technologies are emerging as promising adjuncts in this domain. Although some participants expressed scepticism regarding their clinical utility, digital tools were generally associated with positive emotions when linked to peer support, shared experiences, and the possibility of receiving timely guidance from HCPs. This suggests that eHealth solutions capable of combining interpersonal connection with reliable, personalised content may hold particular promise for enhancing both adherence and psychological well-being. Designing such tools with sensitivity to the lived experience of mBC patients and integrating them meaningfully into the care process will be key to their successful implementation.

The next section presents Study 5, which represents an initial attempt to move in this direction.

4.2 Study 5: Adherence to oral therapies and psychological outcomes in metastatic breast cancer: a pilot evaluation of a multi-component intervention

After reviewing the existing literature on the topic and exploring mBC patients' treatment experiences as expressed in their own words, the next step in this PhD project was to develop an intervention aimed at fostering medication adherence in this specific clinical population.

As previously stated, while several interventions for BC patients have been designed and tested (Heiney et al., 2019), most have focused on adherence to endocrine therapy in early-stage BC, with only a few exceptions addressing mBC or other forms of oral anticancer treatment (Pezzolato, Marzorati, et al., 2023). Furthermore, the limited number of studies examining adherence rates among metastatic cancer patients, coupled with their often conflicting findings (Conley et al., 2022; Delea et al., 2014; Husinka et al., 2021; Komatsu et al., 2020; Yerrapragada et al., 2021), underscores the need to investigate this phenomenon within this population.

To help bridge the gap between early-stage and mBC research, clarify adherence dynamics in this clinical population, and provide direct support for medication-taking behaviour, a pilot optimisation study was conducted using a full factorial design.

4.2.1 Aims of the study

A full factorial pilot optimisation study was conducted with three primary objectives: (1) to evaluate patient satisfaction and the perceived usefulness of every possible combination of three intervention components (i.e., educational material, personalised reminders, and behavioural feedback) developed for mBC patients, (2) to collect data on oral treatment adherence, treatment-related side effects, and relevant psychological variables in this clinical population, and (3) to offer direct support for participants' medication-taking behaviour.

To address objectives (1) and (3), the three components were delivered in all combinations across eight study arms. At the end of the seven-month study period, participants completed a study-specific questionnaire (closed and open items) assessing satisfaction with and perceived utility of the received intervention, and offering space for suggestions to improve the intervention.

To address objective (2), adherence was monitored with a daily self-reported medication diary. Because side effects are frequently associated with non-adherence (Conley et al., 2022; Masiero et al., 2024; Todd et al., 2024), participants were asked to record both their medication-taking and any treatment-related side effects in a daily diary. They also completed a set of validated self-report instruments assessing depressive and anxiety symptoms, quality of life, and beliefs about medicines. These data allowed a detailed characterisation of the mBC sample.

The findings from this study may serve as a foundation for a fully powered optimisation trial, designed to examine both the individual effects of each component and their interactions. Such evidence would provide guidance for the development of an optimised, scalable, and cost-effective intervention.

4.2.2 Material and methods

Study design

A full factorial pilot optimisation study was conducted to evaluate patient satisfaction and the perceived usefulness of a multi-component intervention designed to support adherence to oral anticancer therapies in patients with mBC, to characterise medication adherence and treatment-related side effects in this population, and to provide direct support for participants' medication-taking behaviours. Adherence, side effects, and psychological variables of interest were prospectively monitored at multiple time points across a seven-month follow-up.

As outlined in Section 2.3 of this doctoral thesis, a full factorial design was chosen for its suitability in evaluating multi-component interventions. The intervention comprised

three elements (i.e., educational material, personalised reminders, and behavioural feedback) delivered in all eight possible combinations as shown in Table 11.

Table 11. *Distribution of the intervention components across the eight study conditions.*

Condition	Standard care	Educational material	Reminders	Feedback
1	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	No
3	Yes	Yes	No	Yes
4	Yes	Yes	No	No
5	Yes	No	Yes	Yes
6	Yes	No	Yes	No
7	Yes	No	No	Yes
8	Yes	No	No	No

Allocation was organised so that, for each intervention component, the number of participants receiving it was the same as the number not receiving it. Because the three components were combined in all possible ways, each group (with and without a given component) also included participants who either did or did not receive the other two components, thereby ensuring a balanced distribution across all study conditions.

Following consent, participants were given a unique identifier and assigned to one of the eight conditions according to a pre-generated randomisation list. The list was prepared by the study's statistical team using block randomisation with varying block sizes to maintain balance while limiting predictability. The sequence was generated in R with the *blockrand* package (Snow, 2013).

The study protocol received approval from the Institutional Review Board of IEO (R1862/23–IEO 2014). Written informed consent was obtained from all participants, and all procedures were conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.

Inclusion and exclusion criteria

Patients were eligible for inclusion if they had a confirmed diagnosis of mBC and a current prescription for any oral anticancer agent, including oral chemotherapy, endocrine therapy, or targeted therapy (i.e., cyclin-dependent kinase 4/6 inhibitors, PARP inhibitors). Additionally, requirements included being over 18 years of age, owning a personal smartphone with internet access, demonstrating the willingness and

ability to attend scheduled visits and comply with all study procedures, fluency in Italian, and providing written informed consent.
Patients were excluded if they had psychiatric disorders or other conditions that could compromise their ability to give informed consent, or if they presented comorbidities likely to interfere with adherence to study procedures.

Participants and recruitment

Patients consecutively admitted to the Division of Medical Senology at IEO with a confirmed diagnosis of mBC were approached by one of the authors, who provided an overview of the study. Those who expressed interest were invited to an in-person appointment, where study procedures were explained in greater detail, socio-demographic and clinical data were collected, and informed consent was obtained. Upon signing the consent form, participation was formalised. Each participant was provided with a medication adherence diary and a link to complete an online battery of questionnaire assessing relevant psychological variables. From that day onward, participants were instructed to complete the diary on a daily basis, while the study questionnaires were administered at five predefined time points and sent by email via a dedicated link.

Procedure

The initial in-person appointment outlined above marked the baseline assessment (T0) for each participant. At this stage, they received a set of online psychological questionnaires assessing depressive symptoms (BDI-II), anxiety (STAI-Y), and quality of life (EORTC-QLQ-C30, EORTC-QLQ-BR23). Adherence was monitored using a medication diary, available in paper or digital format, in which participants recorded daily medication intake and, where applicable, the reasons for missed doses (e.g., side effects, forgetfulness, lack of supply). The diary was provided at T0, accompanied by detailed instructions on its completion. After one month (T1), participants returned the first month's diary and were randomly assigned to one of the experimental arms. Follow-up assessments were conducted over the following six months, with adherence and psychological variables measured at three (T2), five (T3), and seven months (T4) from baseline. At T4, in addition to the previously mentioned questionnaires, participants completed an additional questionnaire on their beliefs about medicines (BMQ) and a specifically designed satisfaction and perceived utility questionnaire, the completion of which marked the end of their study participation.

Intervention

The selection of intervention components for this study reflected a balance between the practical constraints of our resources and setting, and the incorporation of techniques that have shown potential in supporting adherence among BC patients. Specifically, the first component—the educational material—was custom-developed as a decision support system for mBC patients (Masiero et al., 2023) within the broader project (i.e., *Enhancing Therapy Adherence Among Metastatic Breast Cancer Patients)* that also included Study 4 (Masiero et al., 2024). The remaining two components, commonly applied in adherence interventions in varying formats, were selected based on BCTs identified in our previous study (Pezzolato, Marzorati, et al., 2023). Indeed, findings from Study 1 suggested that these particular techniques hold promise for fostering adherence to oral medications in BC patients samples. On this basis, it was considered reasonable to test their use in a population of patients with mBC, first to determine whether the interventions would be accepted and perceived as useful, and subsequently to explore whether similar benefits could be observed in this clinical group. These techniques constitute the second and third components of the intervention: personalised reminders and behavioural feedback, both delivered via a widely used messaging platform, WhatsApp. A detailed overview of each intervention component is provided below.

(1) Educational material

The educational material delivers educational content via a web-page in Italian, accessible through a link provided to participants assigned to intervention arms including this component. It is structured into four main sections:

- *Section A. Metastatic breast cancer*: offers information on mBC, including its definition, clinical management, as well as its physical (e.g., pain, weight loss, fatigue) and psychological consequences (e.g., anxiety, depression). It also covers anticancer treatments and the potential side effects and benefits experienced throughout the care pathway;
- *Section B. Adherence to cancer therapies:* explains the concept of non-adherence, its implications, prevalence in oncology populations, and factors influencing medication adherence;
- *Section C. Promoting adherence*: focuses on resources that support adherence, such as personal beliefs, social support, and trust in HCPs, alongside barriers like distress or insufficient knowledge. This section further describes various interventions (educational, affective, and behavioural) aimed at fostering

adherence. It also offers self-management strategies to address potential adherence risks;

- *Section D. My adherence diary*: encourages patients to write a free-text diary where they can record doubts, concerns, reflections, and behaviours related to their illness and treatment, with the option to share these notes with their oncologist during clinical visits.

Content is delivered through a mix of formats including written text, illustrations, flowcharts, graphs and tables. All materials have been carefully reviewed by an expert panel of clinicians and psychologists (Masiero et al., 2023).

When viewed through the lens of the COM-B model (see Chapter 2, section 2.1.1), this component can be hypothesised to act primarily on *reflective motivation*, encouraging patients to reflect on their medication-taking behaviour and to engage with reliable information regarding its necessity and usefulness (Jackson, Eliasson, Barber, et al., 2014).

When applying the BCTT to the educational material, a total of 15 distinct BCTs were identified and coded, including *information about health consequences*, *credible source*, *problem solving* and *goal setting* (Michie et al., 2013). A complete list of the BCTs incorporated into the educational material and the other intervention components is provided in Appendix 7.

(2) Personalised reminders

Personalised reminders were delivered to patients assigned to this intervention component through a common messaging application (WhatsApp). At baseline, participants indicated their therapy plan (i.e., number and frequency of pill intakes, timing, and cycles duration). Based on this information, a researcher scheduled short reminder messages to be sent at the specified times and dates, following the individual therapy schedule. This was managed through *Blueticks* web application (https://blueticks.co). A full list of the messages is provided in Appendix 8a.

Through the lens of COM-B model, this component may primarily influence *psychological capability*, supporting habit formation and reducing the likelihood of unintentional non-adherence due to forgetting (Jackson, Eliasson, Barber, et al., 2014).

When coded using the BCTT, the short messages used as personalised reminders incorporated the BCTs *prompts/cues* and *information about health consequences* (Michie et al., 2013). Notably, these two BCTs were also present in the educational material (see Appendix 7). Although the underlying techniques were conceptually the same, the two components differed substantially in their mode of delivery. In the educational material, participants were encouraged to introduce their own prompts or

cues (for example, setting an alarm) to support adherence and reduce the likelihood of forgetting a dose. In contrast, the personalised reminders delivered these prompts directly to participants via WhatsApp. Similarly, while both components included *information about health consequences*, the educational material provided more detailed and comprehensive explanations, whereas the personalised reminders conveyed this information briefly, highlighting the importance of taking all prescribed medication. Finally, the delivery format clearly distinguished the two components: the educational material was available as a web-page that participants could consult at their discretion, whereas the personalised reminders were actively pushed to participants according to their treatment schedule.

(3) Behavioural feedback

Feedback was delivered via WhatsApp to patients assigned to this intervention component. Participants were asked to send scans of their medication diary every other week (from T1). Within a maximum of two days, a researcher then sent them a specifically designed feedback message. If the patient was found to be adherent to medication (i.e., adherence rate > 80%), they received a "positive" feedback message (i.e., "Great job sticking to your medication schedule! That consistency will really help your medication work how it's supposed to. Keep taking your meds as directed!"). If adherence was below this threshold, they received a "negative" feedback message (i.e., "It seems like you haven't been taking your meds as scheduled. I know it can be hard to remember or make it part of your routine, but consistency is really important for your medication to work properly. If you wish to share any difficulties or obstacles you have encountered, please write to this email address: *********. We will do our best to help you get back on track.").

From a COM-B perspective, this component primarily targets *reflective motivation*, as the feedback was intended to maintain participants' awareness of their medication-taking patterns and to reinforce their intention to follow the prescribed regimen. It also shapes *automatic motivation*, since it provides positive reinforcement when optimal adherence is reported, thereby strengthening the habit of consistent medication use (Jackson, Eliasson, Barber, et al., 2014).

Using BCTT, the content of the behavioural feedback was coded as incorporating the BCTs *feedback on behaviour*, *information about health consequences*, *social support*, and *social reward* (Michie et al., 2013).

Medication Adherence Diary

Adherence was measured using a specifically designed diary, provided in paper or digital format according to patient preference. Patients were asked to complete it

daily, recording the date, whether the medication was taken or missed, and any side effects experienced, with intensity rated on a 0-10 scale. They also noted any other reasons for missed doses. Diaries were collected at T1 and then every two weeks up to T4 (7 months). Adherence was calculated as the percentage of prescribed doses that were taken.

Psychological measures

The following validated questionnaires were administered:

State-Trait Anxiety Inventory (STAI-Y)

The STAI-Y is a self-report measure commonly employed to assess anxiety. It comprises two subscales of 20 items each, allowing the evaluation of acute (state) and chronic (trait) anxiety. Items are rated on a 4-point Likert-type scale, with total scores for each subscale ranging from 20 to 80. The STAI-Y has demonstrated good internal consistency and satisfactory item characteristics (Bergua et al., 2012; Ilardi et al., 2021).

Beck Depression Inventory II (BDI-II)

The BDI-II is one of the most widely used self-report instruments for the assessment of depression (Beck et al., 1996; Wang & Gorenstein, 2013). It includes 21 items assessing depressive symptoms, each rated on a 4-point Likert-type scale from 0 to 3, according to symptom severity over the preceding two weeks. The total score ranges from 0 to 63. Previous studies reported good internal consistency, with Cronbach's α coefficients between 0.83 to 0.96, and good to excellent test-retest reliability coefficients ($0.73 < r < 0.96$). High correlations with other measures of depression and anxiety supported its convergent validity. Furthermore, the BDI-II showed high sensitivity and specificity, confirming its capacity to accurately assess depressive symptomatology (Wang & Gorenstein, 2013).

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)

The EORTC-QLQ-C30 is a self-report instrument consisting of 30 items assessing three domains: functioning (physical, role, cognitive, emotional, and social), symptoms (appetite loss, fatigue, pain, nausea, constipation–diarrhoea, dyspnoea, and insomnia), and global health status/quality of life. Reported Cronbach's α coefficients ranged from 0.56 to 0.85 (Cankurtaran et al., 2008).

European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC-QLQ-BR23)

The EORTC-QLQ-BR23 is a questionnaire designed to evaluate health-related quality of life in patients with BC. It comprises 23 items covering multiple aspects of health, including physical, emotional, sexual, and aesthetic functioning, as well as symptoms specific to BC. Previous evidence indicated good test-retest reliability and satisfactory convergent and discriminant validity for this instrument (Salas et al., 2022; Sprangers et al., 1996).

Beliefs about Medicines Questionnaire (BMQ)

The BMQ is a questionnaire developed in the UK to operationalise the NCF (see Section 2.1.1). The original version consists of two sections, each comprising two subscales. The BMQ-General explores beliefs about medicines in general and comprises two four-item subscales: *overuse*, which reflects perceptions of the excessive prescription of medicines, and *harm*, which captures the representations of medicines as inherently harmful. The BMQ-Specific focuses on medicines prescribed for personal use and contains two subscales: a five-item *necessity* subscale, assessing the perceived need for the prescribed treatment, and a six-item *concerns* subscale, addressing worries or concerns about potential adverse effects of the medication. Each item is rated on a 1 to 5 Likert-type scale. The BMQ-Specific has been used in various clinical populations, including patients with BC, asthma, diabetes, cardiovascular conditions, and psychiatric disorders, and has shown good internal consistency, test-retest reliability, criterion-related validity, and discriminant validity (Grunfeld et al., 2005; Horne et al., 1999).

For the purposes of this study, participants completed the Italian translation of the BMQ-Specific. This translation has documented adequacy, with acceptable internal consistency (Cronbach's $\alpha = 0.78$ for the *necessity* subscale; $\alpha = 0.72$ for the *concerns* subscale) and satisfactory discriminant validity (Argentero et al., 2010).

Satisfaction and perceived utility questionnaire

At the conclusion of the seven-month study, participants were invited to complete a 22-item questionnaire designed to assess both their satisfaction with, and the perceived usefulness of, the different components of the study. All participants were asked to complete three sections of questions common to everyone, as they concerned aspects of the study experienced by all. These addressed the medication diary (perceived utility and satisfaction), any difficulties or limitations encountered during participation, and overall satisfaction with taking part in the study. Items specifically addressing satisfaction with, and the perceived usefulness of, the

intervention components (both individually and as a whole) were completed only by patients who had actually received those components. Closed questions were rated on a 5-point Likert-type scale, while each section also included at least one open question inviting participants to provide suggestions, comments, or critical feedback in their own words.

Sample size justification

The initial sample size calculation indicated that randomising 104 participants (13 per condition), with an expected dropout rate below 10%, would have been sufficient to detect the potential effect of the intervention components on medication adherence. However, recruitment progressed more slowly than anticipated, and preliminary data analyses revealed adherence rates substantially higher than expected. In light of these findings, the decision was made to discontinue recruitment before reaching the planned sample size. A final sample of 32 participants was considered adequate to address the exploratory aims outlined in the dedicated section.

Statistical analysis

The primary outcome of this study was adherence to oral medication in patients with mBC, assessed as the proportion of prescribed pills taken during the seven-month follow-up. Adherence rates, with 95% confidence intervals, were estimated using a binomial model for each time-point across the entire sample. Adherence was further examined by grouping participants based on whether or not they had received each intervention component. When adherence data were available only for a partial observation window (e.g., 25 out of 28 days), the measure was set to missing if the available days covered less than 80% of the expected period. For patients who discontinued oral therapy for clinical reasons in agreement with the healthcare team (n = 3), follow-up was censored at the time of treatment discontinuation.

Treatment-related side effects were self-reported by participants in diaries, where they indicated the type, frequency, and perceived intensity on a 0-10 scale. Monthly rates of side effects were estimated using a negative binomial model with 95% confidence intervals, dividing the total number of reported events within each category by the number of months with available data. This strategy allowed the use of all available information, including data from patients who did not complete diaries for the entire study duration. In addition, the proportions of patients reporting at least one symptom in each side effect category was calculated. With respect to symptom intensity, for each side effect type, mean intensity was computed as the sum of reported values divided by the number of events for which an intensity score was available. Only

participants with at least one event in the respective category were included in this analysis.

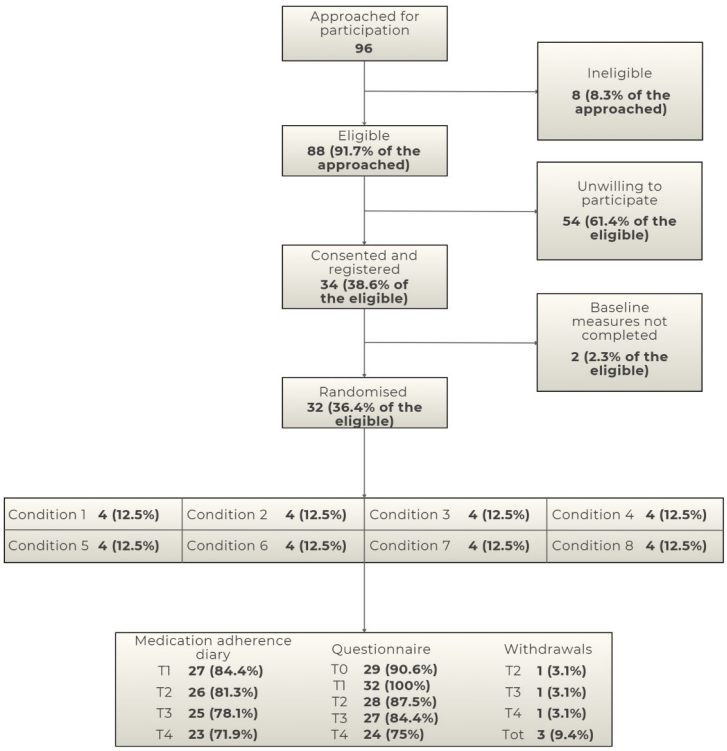
Regarding psychological variables (i.e., anxiety, depressive symptoms, quality of life, and beliefs about medicines), descriptive statistics were reported together with distributions at different time-points, where available. Finally, descriptive statistics were also calculated for participants' answers to the questionnaire on satisfaction and perceived usefulness questionnaire.

4.2.3 Results

Participants

Among the patients with mBC receiving care at the Division of Medical Senology at IEO, 96 women were approached and invited to participate in the study. Eight did not meet the eligibility criteria: two had discontinued oral therapies, two lacked sufficient fluency in Italian, two did not have or were unable to use WhatsApp, one was already enrolled in another non-compatible trial, and one had other conditions that prevented adherence to study procedures. Of the remaining 88 eligible patients, 54 (61.4%) declined participation, most often citing personal circumstances, lack of time, or a general lack of interest. The remaining 34 (38.6%) agreed to enrol and were recruited. Among these, two did not complete any questionnaires or return medication adherence diaries and were therefore excluded from the analyses, leaving 32 participants available for data analysis.

Figure 7. *Study 5, CONSORT flowchart of patient recruitment and study participation.*



Participants were equally distributed across study conditions, but three withdrew during the trial due to changes in their treatment plan that required discontinuation of oral therapy (one before T2, one before T3, and one before T4). Among those who completed the study, some data remained incomplete: several participants failed to return their medication adherence diaries (from 84.4% at T1 to 71.9% at T4), and, to a lesser extent, some did not complete the questionnaires (from 100% at T1 to 75% at T4).

Sample characteristics

Participants ranged in age from 35 and 73 years, with a median of 59.5. The majority were married or cohabiting (*n* = 25; 78.1%), and nearly all had completed at least an upper secondary education (*n* = 30; 93.8%). More than half were working at the time of the study (*n* = 18; 56.3%), while approximately one third were retired (*n* = 10; 31.3%). Regarding treatment, the most frequently prescribed oral therapy was chemotherapy (i.e., abemaciclib, capecitabine, cyclophosphamide), reported by 14 participants (43.8%). This was followed by endocrine therapy combined with a targeted agent (i.e., letrozole with palbociclib or ribociclib; *n* = 11; 34.4%), and by targeted therapy alone (i.e., palbociclib, ribociclib, talazoparib; *n* = 7; 21.9%).
Sample characteristics are presented in Table 12.

Table 12. *Sample characteristics.*

Variable	**Level**	**Overall (*N* = 32)**
Age at eligibility, median (min-max)		59.5 (35-73)
Marital status, *N* (%)	Single	3 (9.4)
	Cohabiting	5 (15.6)
	Married	20 (62.5)
	Divorced or separated	1 (3.1)
	Widowed	3 (9.4)
Education level, *N* (%)	Lower secondary school	2 (6.3)
	Upper secondary school	14 (43.8)
	Bachelor’s degree	1 (3.1)
	Master’s degree	14 (43.8)
	Postgraduate training	1 (3.1)
Occupation, *N* (%)	Unemployed	1 (3.1)

Variable	Level	Overall (*N* = 32)
	Employed	15 (46.9)
	Self employed	3 (9.4)
	Homemaker	3 (9.4)
	Retired	10 (31.3)
Children, *N* (%)	No	11 (34.4)
	Yes	21 (65.6)
Years since first diagnosis, median (min-max)		8.2 (2.0-23.8)
	Missing	1
Previous oral therapy since mBC diagnosis, *N* (%)	No	4 (12.5)
	Yes	28 (87.5)
Type of current oral therapy, *N* (%)	Oral chemotherapy	14 (43.8)
	ET + targeted therapy	11 (34.4)
	Targeted therapy	7 (21.9)

ET = endocrine therapy

Medication adherence

Adherence was assessed using participants' medication diaries and calculated as the percentage of prescribed doses actually taken. Medication diaries were considered valid only if they covered at least 80% of the days between two time-points; when this threshold was not met, the data were treated as missing. Overall, adherence rates were remarkably high, exceeding initial expectations, with very few missed doses: adherence ranged from 98.9% at T1 to 98.6% at T4.

Table 13 summarises overall adherence rates across all time-points.

Table 13. *Adherence percentage at the four time-points.*

Time-point	N	Missing	Total assumed	Total prescribed	Adherence (%)	95% CI
T1 (1 month)	27	5	2049	2072	98.9	98.3-99.3
T2 (3 months)	26	6	4307	4349	99.0	98.7-99.3
T3 (5 months)	25	7	4037	4076	99.0	98.7-99.3
T4 (7 months)	23	9	3156	3202	98.6	98.1-98.9

CI = confidence interval

When the sample was divided according to exposure to the individual intervention components, adherence remained constantly high across both groups and time-points, ranging from 98.1% to 99.5%, with no significant differences observed. A detailed summary of adherence rates for each component condition is provided in Appendix 9.

Side effects

Side effects were reported through the medication diaries, where participants were asked to record type, frequency and intensity of side effects for each day of the week. The individual side effects reported were subsequently grouped into 12 broader categories: gastrointestinal symptoms; constitutional/systemic symptoms; musculoskeletal/osteoarticular pain and symptoms; cutaneous and dermatological symptoms; psycho-emotional symptoms; mouth, taste, and smell alterations; symptoms involving nose, throat, and eyes; aesthetic and metabolic alterations; vasomotor and cardiovascular symptoms; vertigo and dizziness; sensory symptoms; and respiratory symptoms. The specific symptoms included within each category are listed in Table 14.

Table 14. *Overview of side effect categories and related reported side effects.*

Side effect categories	Reported side effects
Gastrointestinal symptoms	Nausea, vomiting, gastric disturbances, abdominal bloating, diarrhoea, bowel disturbances, abdominal colic, constipation, frequent bowel movements, stomach heaviness.
Constitutional/systemic symptoms	General discomfort, fatigue, headache, sleepiness, chills, anaemia, swollen lymph nodes.
Musculoskeletal/osteoarticular pain and symptoms	Pain, joint pain, bone pain, back pain, cramps, joint stiffness, reduced mobility.
Cutaneous and dermatological symptoms	Cracks on hands and feet, dry skin, skin rash, itching, swelling (limbs, face), scalp crusts, hand-foot syndrome.
Psycho-emotional symptoms	Insomnia, feelings of emptiness, mental heaviness, restlessness, memory problems.
Mouth, taste, and smell alterations	Dysphagia, mouth disorders, altered taste, bad breath.
Symptoms involving nose, throat, and eyes	Dry nose and throat, conjunctivitis, eye burning, watery eyes.
Aesthetic and metabolic alterations	Hair loss, excess hair growth, weight gain.
Vasomotor and cardiovascular symptoms	Hot flushes, palpitations.

Side effect categories	Reported side effects
Vertigo and dizziness	Dizziness, vertigo.
Sensory symptoms	Blurred vision, vision loss, hearing loss.
Respiratory symptoms	Dyspnoea, cough.

Regarding side effects, analysable data were available for 27 participants. Of these, 20 (74.1%) reported at least one side effect. The most frequently reported category was constitutional/systemic symptoms (e.g., fatigue, headache, general discomfort), experienced by 16 participants (59.3%). Gastrointestinal symptoms (e.g., nausea, diarrhoea, constipation) were reported by 13 participants (48.1%). Musculoskeletal/osteoarticular pain and symptoms were the third most frequent category (*n* = 10; 37%), followed by cutaneous and dermatological symptoms (*n* = 7; 25.9%). All other categories were reported by fewer than 20% of participants.

When considering the distribution of individual events rather than the proportion of patients, the same four categories remained the most frequently observed, though in a slightly different order. Constitutional/systemic symptoms were again the most frequently reported (24.5% of all reported events), followed by musculoskeletal/osteoarticular pain and symptoms (20%), cutaneous and dermatological symptoms (19%), and gastrointestinal symptoms (18.6%). Together, these four categories accounted for 82.1% of all reported events. The frequencies and percentages of side effect categories are summarised in Table 15.

Table 15. *Overview of side effect categories and related reported side effects.*

Side effect categories	Patients with at least one event, *n* (%)	Total events, *n* (% of total events)
Gastrointestinal symptoms	13 (48.1)	840 (18.6)
Constitutional/systemic symptoms	16 (59.3)	1105 (24.5)
Musculoskeletal/osteoarticular pain and symptoms	10 (37)	903 (20.0)
Cutaneous and dermatological symptoms	7 (25.9)	857 (19.0)
Psycho-emotional symptoms	5 (18.5)	54 (1.2)
Mouth, taste, and smell alterations	3 (11.1)	92 (2.0)
Symptoms involving nose, throat, and eyes	4 (14.8)	184 (4.1)
Aesthetic and metabolic alterations	4 (14.8)	230 (5.1)
Vasomotor and cardiovascular symptoms	5 (18.5)	221 (4.9)

Side effect categories	Patients with at least one event, *n* (%)	Total events, *n* (% of total events)
Vertigo and dizziness	3 (11.1)	4 (0.1)
Sensory symptoms	2 (7.4)	10 (0.2)
Respiratory symptoms	2 (7.4)	11 (0.2)
No side effects	7 (25.9)	/
Total	20 (74.1)	4511 (100.0)

Similarly, when examining monthly rates across side effects categories, systemic and constitutional symptoms showed the highest monthly rate, followed by musculoskeletal/osteoarticular pain and symptoms, cutaneous and dermatological symptoms, and gastrointestinal symptoms. A comprehensive presentation of monthly rates for all side effect categories is presented in Table 16, while the detailed distribution of adverse events according to specific side effect is reported in Appendix 10.

Table 16. *Monthly rates of side effect events by symptom category (n = 27).*

Side effect categories	Side effect event per month	95% CI
Gastrointestinal symptoms	4.59	1.61-13.1
Constitutional/systemic symptoms	6.11	2.48-15.0
Musculoskeletal/osteoarticular pain and symptoms	5.19	1.40-19.2
Cutaneous and dermatological symptoms	4.60	0.84-25.2
Psycho-emotional symptoms	0.30	0.06-1.42
Mouth, taste, and smell alterations	0.51	0.05-5.71
Symptoms involving nose, throat, and eyes	0.99	0.11-8.82
Aesthetic and metabolic alterations	1.28	0.14-11.9
Vasomotor and cardiovascular symptoms	1.17	0.17-8.05
Vertigo and dizziness	0.02	0.01-0.07
Sensory symptoms	0.07	0.01-0.72

Side effect categories	Side effect event per month	95% CI
Respiratory symptoms	0.06	0.01-0.57

CI = confidence interval

Regarding side effect intensity, mean scores by category on a 0-10 scale ranged from 5.0 (cutaneous and dermatological symptoms) to 8.1 (respiratory symptoms). Using interpretation thresholds whereby scores from 4.0 to 6.9 are considerate moderate and scores higher or equal than 7.0 severe, most side effect categories fall within the moderate range. The only exceptions were sensory and respiratory symptoms, with mean intensities of 7.7 and 8.1, respectively, which lie in the severe range. Importantly, these two categories were uncommon: together they account for only 0.4% of all reported side effect events, and each was reported at least once by only two participants. Because the mean intensities for these categories are driven by very few events and participants, those estimates should be interpreted with caution. A detailed summary of side effect intensities by categories is reported in Table 17.

Table 17. *Mean intensity of reported side effects by symptom category (0-10 scale).*

Side effect category	Mean intensity reported					
	n	Mean	SD	Median	Q1	Q3
Gastrointestinal symptoms	13	5.9	1.4	6.0	5.0	6.6
Constitutional/systemic symptoms	15	5.9	1.4	6.0	4.0	7.0
Musculoskeletal/osteoarticular pain and symptoms	10	6.7	1.4	6.8	5.7	7.9
Cutaneous and dermatological symptoms	7	5.0	1.7	5.1	3.5	7.1
Psycho-emotional symptoms	5	6.4	2.3	7.1	5.0	7.8
Mouth, taste, and smell alterations	3	6.5	0.9	7.0	5.5	7.0
Symptoms involving nose, throat, and eyes	4	5.7	2.5	5.9	3.6	7.8
Aesthetic and metabolic alterations	4	5.5	1.2	5.6	4.6	6.4
Vasomotor and cardiovascular symptoms	5	5.9	1.7	6.5	5.8	7.1
Vertigo and dizziness	2	6.0	1.4	6.0	5.0	7.0
Sensory symptoms	2	7.7	0.5	7.7	7.3	8.0

Side effect category	Mean intensity reported					
	n	Mean	SD	Median	Q1	Q3
Respiratory symptoms	2	8.1	0.1	8.1	8.0	8.2

SD = standard deviation

Psychological variables

Anxiety was assessed using the STAI-Y. Form 1 (state anxiety) was administered at all time-points, whereas Form 2 (trait anxiety) was completed only at baseline, since trait anxiety is a relatively stable characteristic not expected to vary substantially over the study period. Across the full sample, median and mean STAI-Y scores at each time-point fell within the mild range (40-50) (Barisone et al., 2004), ranging from 41.5 to 44.5 (median), and from 41.8 to 44.4 (mean). Consistent with these central tendency measures, examination of score distributions across the predefined categories (i.e., non-pathological, mild, moderate, and severe), showed that at least 60% of participants, at every time-point and for both STAI-Y forms, scored in the non-pathological or mild ranges. Detailed descriptive statistics are reported in Table 18, and the distribution of scores by category is summarised in Table 19.

Table 18. *Descriptive statistics of STAI-Y state and trait anxiety scores across time-points.*

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
STAI-Y1	**T0 (baseline)**	30	2	42	41.9	10.4	21	59
	T1 (1 month)	32	0	43.5	42.5	10.5	21	60
	T2 (3 months)	28	4	44.5	44.4	11.9	24	64
	T3 (5 months)	27	5	43	42.7	11.3	23	68
	T4 (7 months)	24	8	41.5	41.8	10	20	57
STAI-Y2	**T0 (baseline)**	29	3	42	43.3	10.2	22	64

SD = standard deviation

Table 19. *Distribution of STAI-Y state and trait anxiety scores across severity ranges.*

Questionnaire	Time-point	Level	Overall (*N* = 32)
STAI-Y form 1 (how do you feel now, that is, at this moment?)	**T0**	Non-pathological	13 (43)
		Mild	10 (33)
		Moderate	7 (23)
		Severe	0 (0)
		Missing	2
	T1	Non-pathological	12 (38)
		Mild	12 (38)
		Moderate	8 (25)
		Severe	0 (0)
	T2	Non-pathological	11 (39)
		Mild	6 (21)
		Moderate	8 (29)
		Severe	3 (11)
		Missing	4
	T3	Non-pathological	11 (41)
		Mild	10 (37)
		Moderate	5 (19)
		Severe	1 (4)
		Missing	5
	T4	Non-pathological	10 (42)
		Mild	8 (33)
		Moderate	6 (25)
		Severe	0 (0)
		Missing	8
STAI-Y form 2 (how do you usually feel?)	**T0**	Non-pathological	10 (34)
		Mild	12 (41)
		Moderate	6 (21)
		Severe	1 (3)

Questionnaire	Time-point	Level	Overall (*N* = 32)
		Missing	3

Depressive symptoms, as measured by the BDI-II, were even lower, indicating that such symptoms were experienced only sporadically, if at all, by the study sample. Median and mean scores at each time-point fell within the minimal range, the lowest possible category, ranging from 9 to 11.5 and 10.3 to 12.7, respectively (≤13 = minimal level). This low prevalence was further supported by the distribution analyses, which showed that at least 57% of participants fell within the minimal level category at all time-points. Detailed descriptive statistics are presented in Table 20, and the distribution of scores by category is summarised in Table 21.

Table 20. *Descriptive statistics of BDI-II depressive symptoms scores across time-points.*

	Time-point	n	Missing	Median	Mean	SD	Min	Max
BDI-II	**T0 (baseline)**	29	3	11	11.8	8.3	0	31
	T1 (1 month)	32	0	9.5	11.4	8.5	0	29
	T2 (3 months)	28	4	11.5	12.7	9.6	0	32
	T3 (5 months)	27	5	9	10.6	8.9	0	33
	T4 (7 months)	24	8	9.5	10.3	7.7	0	27

SD = standard deviation

Table 21. *Distribution of BDI-II depressive symptoms scores across severity ranges.*

Questionnaire	Time-point	Level	Overall (*N* = 32)
BDI-II	**T0**	Minimal level	19 (66)
		Mild level	4 (14)
		Moderate level	4 (14)
		Severe level	2 (7)
		Missing	3

Questionnaire	Time-point	Level	Overall (*N* = 32)
	T1	Minimal level	20 (63)
		Mild level	6 (19)
		Moderate level	5 (16)
		Severe level	1 (3)
	T2	Minimal level	16 (57)
		Mild level	5 (18)
		Moderate level	5 (18)
		Severe level	2 (7)
		Missing	4
	T3	Minimal level	19 (70)
		Mild level	5 (19)
		Moderate level	1 (4)
		Severe level	2 (7)
		Missing	5
	T4	Minimal level	15 (63)
		Mild level	7 (29)
		Moderate level	2 (8)
		Severe level	0 (0)
		Missing	8

Regarding quality of life as measured with the EORTC-QLQ-C30, scores observed in this study were broadly comparable with the published reference values for patients with mBC (Scott et al., 2008). Using a conventional minimal important difference (MID) of 10 points (Osoba et al., 1998), meaningful differences were observed in two functioning scales. Role functioning was higher in our sample (means 79-82.8; medians 83-91.5) compared with the reference values (mean 67.4; median 66.7), exceeding the MID. Emotional functioning (means 75.3-80.4; medians 75-83) was likewise higher than the reference mean (65.9; median 66.7), with differences across time-points that approached or in some instances exceeded the MID. This indicates that our sample reported better preservation of daily activities and greater emotional well-being compared with the reference population.

Improved scores (indicating fewer or less bothersome symptoms) were also found for three symptom scales: pain (means 11.1-16.7; medians 0-17; reference mean 30.9; median 33.3), appetite loss (means 8-11.9; median 0; reference mean 21.7; median 0), and financial difficulties (means 7.1-9.7; median 0; reference mean 18.6; median 0). These results point to a nuanced picture, with better role and emotional functioning and fewer physical complaints in some domains, such as pain and appetite loss, but overall comparable quality of life to that of the reference population.

Descriptive statistics for quality of life as assessed by the EORTC-QLQ-C30 are presented in Table 22.

Table 22. *Descriptive statistics of EORTC-QLQ-C30 scores across time-points.*

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
Global health status / QoL	**T0 (baseline)**	29	3	67	64.6	16	33	100
	T1 (1 month)	31	1	67	61.6	15.6	17	92
	T2 (3 months)	28	4	58	59.5	14.8	33	83
	T3 (5 months)	27	5	58	63.9	14	50	100
	T4 (7 months)	24	8	62.5	59.7	16.9	33	92
Physical functioning	**T0 (baseline)**	29	3	80	79.3	16.6	27	100
	T1 (1 month)	31	1	87	79.1	17.3	33	100
	T2 (3 months)	28	4	80	79	16	53	100
	T3 (5 months)	27	5	80	80.7	14.2	53	100
	T4 (7 months)	24	8	80	80.9	14.4	47	100
Role functioning	**T0 (baseline)**	29	3	83	82.8	20.6	33	100
	T1 (1 month)	31	1	83	79	21.5	33	100
	T2 (3 months)	28	4	91.5	81	22.1	33	100

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
	T3 (5 months)	27	5	83	82.7	19.8	50	100
	T4 (7 months)	24	8	83	79.2	20.4	33	100
Emotional functioning	**T0 (baseline)**	29	3	75	79.3	15.5	42	100
	T1 (1 month)	31	1	83	80.4	15.1	50	100
	T2 (3 months)	28	4	75	75.3	19	33	100
	T3 (5 months)	27	5	83	78.1	18.4	33	100
	T4 (7 months)	24	8	83	79.9	16.9	50	100
Cognitive functioning	**T0 (baseline)**	29	3	100	86.7	18.6	33	100
	T1 (1 month)	31	1	83	85.4	15.3	50	100
	T2 (3 months)	28	4	83	83.3	20.3	33	100
	T3 (5 months)	27	5	100	90.1	12.4	67	100
	T4 (7 months)	24	8	83	86	16.1	33	100
Social Functioning	**T0 (baseline)**	29	3	83	81	22.2	33	100
	T1 (1 month)	31	1	83	80.7	18.7	33	100
	T2 (3 months)	28	4	83	82.7	18.4	33	100
	T3 (5 months)	27	5	83	80.2	22.7	33	100
	T4 (7 months)	24	8	83	79.8	20.2	33	100
Fatigue	**T0 (baseline)**	29	3	33	33.6	19.9	0	78

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
	T1 (1 month)	31	1	33	35.3	17.9	0	78
	T2 (3 months)	28	4	33	34.4	20.5	0	67
	T3 (5 months)	27	5	33	33.2	19.8	0	67
	T4 (7 months)	24	8	33	31.8	23.3	0	78
Nausea and vomiting	**T0 (baseline)**	29	3	0	5.2	9.1	0	33
	T1 (1 month)	31	1	0	6.5	10.3	0	33
	T2 (3 months)	28	4	0	9.5	13.1	0	33
	T3 (5 months)	27	5	0	7.4	11.6	0	33
	T4 (7 months)	24	8	0	9	15.4	0	50
Pain	**T0 (baseline)**	29	3	0	13.2	20.1	0	67
	T1 (1 month)	31	1	17	15.1	17.4	0	67
	T2 (3 months)	28	4	8.5	16.7	21.3	0	67
	T3 (5 months)	27	5	0	12.3	15.7	0	50
	T4 (7 months)	24	8	0	11.1	17.4	0	50
Dyspnoea	**T0 (baseline)**	29	3	0	17.2	21.1	0	67
	T1 (1 month)	31	1	0	18.2	20.7	0	67
	T2 (3 months)	28	4	33	21.3	20.7	0	67
	T3 (5 months)	27	5	33	19.6	21.2	0	67

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
	T4 (7 months)	24	8	0	13.8	19.4	0	67
Insomnia	**T0 (baseline)**	29	3	33	24	26.6	0	100
	T1 (1 month)	31	1	33	23.5	21.4	0	67
	T2 (3 months)	28	4	33	26.1	29.3	0	100
	T3 (5 months)	27	5	33	24.6	25.5	0	67
	T4 (7 months)	24	8	33	27.7	25.5	0	67
Appetite loss	**T0 (baseline)**	29	3	0	8	17	0	67
	T1 (1 month)	31	1	0	10.7	20	0	67
	T2 (3 months)	28	4	0	11.9	20.7	0	67
	T3 (5 months)	27	5	0	9.8	15.4	0	33
	T4 (7 months)	24	8	0	11	15.9	0	33
Constipation	**T0 (baseline)**	29	3	0	21.8	32.5	0	100
	T1 (1 month)	31	1	0	22.5	27.8	0	100
	T2 (3 months)	28	4	16.5	24.9	31	0	100
	T3 (5 months)	27	5	0	12.3	22.8	0	100
	T4 (7 months)	24	8	0	20.7	27.5	0	100
Diarrhoea	**T0 (baseline)**	29	3	0	6.8	13.6	0	33
	T1 (1 month)	31	1	0	7.5	14	0	33

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
	T2 (3 months)	28	4	0	13	18.8	0	67
	T3 (5 months)	27	5	0	8.6	17.5	0	67
	T4 (7 months)	24	8	0	8.2	14.6	0	33
Financial difficulties	**T0 (baseline)**	29	3	0	9.1	21.6	0	100
	T1 (1 month)	31	1	0	7.5	14	0	33
	T2 (3 months)	28	4	0	7.1	13.8	0	33
	T3 (5 months)	27	5	0	8.6	14.7	0	33
	T4 (7 months)	24	8	0	9.7	18.3	0	67

SD = standard deviation; QoL = quality of life.

When examining quality of life through the BC-specific module EORTC-QLQ-BR23, the results observed in this study were again broadly in line with the available reference values for patients with mBC (Scott et al., 2008). Considering, as in the previous analysis, the conventional MID of 10 points (Osoba et al., 1998), meaningful differences emerged in two functioning domains. In the body image domain, where higher scores indicate a more positive perception of one's appearance, our participants reported lower values (means 68.2-73.5; medians 67-83) than the reference population (mean 81.9; median 91.7). Sexual enjoyment showed some variation across time-points, with our participants reporting means of 40.4-66.7 and medians of 33-67, compared with reference values of mean 55.1 and median 66.7.

Differences exceeding the MID were also found in three symptom domains. Our sample reported lower scores for breast symptoms (means 4.3-8.6; median 0; reference mean 17.6; median 16.7) and arm symptoms (means 8.1-11; median 0; reference mean 21.0; median 22.2), while considerably higher scores were observed for distress related to hair loss (means 40.9-51.9; medians 33-67) compared with the reference values (mean 5.3; median 0). These findings suggest a mixed picture, with lower symptom burden in some physical domains but greater psychosocial distress related to body image and hair loss.

Descriptive statistics for quality of life as measured by the EORTC-QLQ-BR23 are presented in Table 23.

Table 23. *Descriptive statistics of EORTC-QLQ-BR23 scores across time-points.*

	Time-point	N	Missing	Median	Mean	SD	Min	Max
Body image	**T0 (baseline)**	29	3	75	71.8	25.6	0	100
	T1 (1 month)	32	0	79	71.1	28.5	0	100
	T2 (3 months)	28	4	67	68.2	27.5	8	100
	T3 (5 months)	27	5	75	73.5	26.8	0	100
	T4 (7 months)	24	8	83	72.6	29.4	0	100
Sexual functioning	**T0 (baseline)**	29	3	0	19	24.3	0	67
	T1 (1 month)	32	0	0	16.1	22.9	0	83
	T2 (3 months)	28	4	0	14.2	20.1	0	67
	T3 (5 months)	27	5	17	21	27.2	0	100
	T4 (7 months)	24	8	0	21.5	28.5	0	100
Sexual enjoyment	**T0 (baseline)**	12	20	67	66.7	24.7	33	100
	T1 (1 month)	14	18	33	40.4	23.5	0	67
	T2 (3 months)	11	21	33	48.4	31.3	0	100
	T3 (5 months)	13	19	33	51.2	26.1	33	100
	T4 (7 months)	11	21	33	51.4	27.5	33	100
Future perspective	**T0 (baseline)**	29	3	67	54.1	33.9	0	100
	T1 (1 month)	32	0	67	53.2	31.6	0	100

	Time-point	N	Missing	Median	Mean	SD	Min	Max
	T2 (3 months)	28	4	67	51.2	30.9	0	100
	T3 (5 months)	27	5	67	50.6	33.9	0	100
	T4 (7 months)	24	8	50	52.7	32.6	0	100
Systemic therapy side effects	**T0 (baseline)**	29	3	14	15.8	10	0	43
	T1 (1 month)	32	0	19	18.3	9.7	5	43
	T2 (3 months)	28	4	14	16.8	10.2	5	38
	T3 (5 months)	27	5	14	17.9	11.4	5	38
	T4 (7 months)	24	8	14	17.7	13.5	0	52
Breast symptoms	**T0 (baseline)**	29	3	0	6.3	10.6	0	33
	T1 (1 month)	32	0	0	8.6	12.7	0	42
	T2 (3 months)	28	4	0	8	12.4	0	42
	T3 (5 months)	27	5	0	4.3	6.7	0	25
	T4 (7 months)	24	8	0	7.2	12	0	33
Arm symptoms	**T0 (baseline)**	29	3	0	11	13.5	0	44
	T1 (1 month)	32	0	0	9.3	13.5	0	56
	T2 (3 months)	28	4	0	9.1	15.4	0	67
	T3 (5 months)	27	5	0	8.1	13.8	0	44
	T4 (7 months)	24	8	0	9.2	14.4	0	44

	Time-point	N	Missing	Median	Mean	SD	Min	Max
Upset by hair loss	T0 (baseline)	10	22	33	49.9	23.8	33	100
	T1 (1 month)	13	19	33	40.9	27.9	0	100
	T2 (3 months)	9	23	67	51.9	37.8	0	100
	T3 (5 months)	9	23	33	51.8	33.9	0	100
	T4 (7 months)	9	23	33	44.4	33.5	0	100

SD = standard deviation

At the end of the study, 26 participants completed the BMQ. This made it possible to characterise patients' beliefs about their oral anticancer therapy, specifically the *necessity* and *concerns* constructs. Necessity scores were generally high (subscale range 5-25; min-max = 14-25; mean = 21.6; median = 22; SD = 2.9), indicating that respondents tended to view their medication as important and needed for their health. By contrast, concerns showed a lower mean and greater variability (subscale range 6-30; min-max = 6-23; mean = 15; median = 15.5; SD = 4.3), suggesting more heterogeneous levels of worry about potential harms or adverse effects within this sample.

When examining the balance between perceived necessity and treatment-related concerns through the necessity-concerns differential, the results suggested that necessity generally outweighed concerns. The mean differential was 6.5, with a median of 7 (SD = 5.2). Only three participants (11.5%) reported higher levels of concern than perceived necessity.

Descriptives statistics for the BMQ are reported in Table 24.

Table 24. *Descriptive statistics of BMQ scores across time-points.*

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
BMQ	Necessity	26	6	22	21.6	2.9	14	25
	Concerns	26	6	15.5	15	4.3	6	23

	Time-point	*n*	Missing	Median	Mean	SD	Min	Max
	N-C	26	6	7	6.5	5.2	-3	19

SD = standard deviation; N-C = necessity-concerns differential.

Patient satisfaction and perceived utility

Concerning the satisfaction and perceived usefulness questionnaire, all items were answered on a five-point Likert-type scale, where higher scores indicated a positive judgement of the intervention features and study participation (e.g., perceived usefulness, satisfaction, clarity, ease of use). The only exception was a question on assessing whether participants had read the educational material, for which a score of 1 indicated a positive response and 0 a negative one.

Overall, participants rated the intervention components as useful and satisfactory, with median scores ranging from 4 to 5 for all questions. Slightly lower ratings were observed for the perceived usefulness of the diaries, educational material, and behavioural feedback, as well as for satisfaction with the diaries, with mean scores remaining above 3.8, thus consistently falling within the "positive half" of the scale. Particularly high ratings were given to questions regarding participation in the study, with medians of five across the three items and mean scores exceeding 4.5. These results indicate that participants generally found the study procedures easy to follow, the time commitment appropriate, and the experience comfortable. A comprehensive summary of the questionnaire results is presented in Table 25.

Table 25. *Descriptive statistics of patient satisfaction and perceived utility questionnaire.*

	Item	n	Missing	Median	Mean	SD	Min	Max
Medication diaries (*N* = 32)	**Was keeping the diaries useful in supporting your adherence?**	25	7	4	3.8	1.2	1	5

	Item	n	Missing	Median	Mean	SD	Min	Max
	How satisfied are you with the diaries?	25	7	4	3.8	1.1	1	5
Educational material / DSS (*n* = 16)	**Did you read the material?**	14	2	1	0.9	0.4	0	1
	How clear was it?	13	3	5	4.5	1.1	1	5
	Was it useful?	13	3	4	3.9	1.2	1	5
	How satisfied are you with it?	13	3	5	4.2	1.2	1	5
Personalised reminders (*n* = 16)	**Where the reminders useful in supporting your adherence?**	13	3	4	4.2	0.8	3	5
	How satisfied are you with them?	13	3	4	4.2	0.9	3	5
Behavioural feedback (*n* = 16)	**Was the feedback useful in supporting your adherence?**	10	6	4	3.8	0.8	3	5
	How satisfied are you with it?	10	6	4	4.2	0.6	3	5

	Item	n	Missing	Median	Mean	SD	Min	Max
Whole intervention (*n* = 28)	**Did the intervention meet your needs?**	22	6	4	4.1	0.8	2	5
	Do you think it could be beneficial for others in a similar condition?	22	6	4.5	4.3	0.8	2	5
Study participation (*N* = 32)	**How easy was it for you to take part in the study?**	25	7	5	4.6	0.7	3	5
	Did you feel comfortable while participating?	25	7	5	4.6	0.7	3	5
	Was the time commitment adequate?	25	7	5	4.5	0.8	3	5

SD = standard deviation

Finally, the open-ended questions included in the satisfaction and perceived utility questionnaire provided valuable insights in participants' own words.

Regarding the medication diaries, the most frequent suggestions for improvement concerned creating a digital version, such as an app (*n* = 3), to enhance usability, or adding features (i.e., automatic submission to HCPs, inclusion of selectable list of possible side effects). Other suggestions reflected difficulties encountered while completing the diaries, including the limited space available in the paper format, uncertainty about whether certain symptoms were related to the treatment or other causes, and challenges in completing them consistently on time. One participant noted that diaries may only be useful for a limited period, sufficient to raise awareness of the

need to take medication, while another emphasised the value of providing in-person psychological support to all cancer patients.

For the educational material, no suggestions were offered regarding content or clarity, although one participant again highlighted the usefulness of in-person psychological support.

Similarly, participants largely expressed satisfaction with the personalised reminders, with only one suggesting their integration into a digital app alongside the diaries.

No suggestions for improvements were reported regarding the behavioural feedback.

When asked about the most useful aspects of the interventions, most participants cited elements related to interactions and relationships with the research staff (*n* = 5; e.g., feeling listened to, reassured, supported, and involved in self-care), the personalised reminders (*n* = 4), or the medication diaries (*n* = 3). One participant identified feedback as the most valuable component, while another highlighted the questionnaires for fostering reflection on their condition. Another participant noted that the intervention generally helped maintain attention to therapy.

Conversely, when asked about the least helpful aspects or any difficulties experienced during participation, participants mainly reported challenges with diary completion in general (*n* = 1), particularly due to the paper format (*n* = 3), or with submitting completed diaries to the researchers (*n* = 1). One participant remarked that the questionnaires lacked an option to indicate improvement in their condition, and another stressed that in-person meetings would have been beneficial.

Finally, regarding perceived study limitations, participants suggested the need for in-person meetings to receive additional support (*n* = 2) or, at minimum, the opportunity to speak with a physician as part of the intervention (*n* = 1). Two participants noted difficulties or negative effects associated with writing about their condition and side effects, while another two reiterated previous points, including the absence of an option to report improvements and challenges with the paper format. One participant indicated that they did not feel the intervention was necessary, as they were already diligent and consistent in taking their therapy.

Examples of participants' answers are presented in Table 26, with the full set of responses provided in Appendix 11.

In conclusion, the findings from the open-ended questions align with those reported in the closed questions, are consistent with the high adherence rates observed, and support the potential explanations discussed in the following section.

Table 26. *Examples of participants' responses to the satisfaction and perceived utility questionnaire.*

	Item	n	Missing	No suggestions	Examples of answers
Medication diaries (*N* = 32)	**Suggestions**	17	15	10	"I would have created a diary via an app or in digital form. I find it an easier tool to manage than paper sheets." "I had some doubts when describing side effects (for me, only fatigue), especially when they might have also been caused by other factors (occasional illness, flu, etc.)."
Educational material / DSS (*n* = 16)	**Clarity/ improvement**	5	11	4	"There was a lack of in-person meetings with a psychologist to also explore one's personal psychological state, not only aspects related to the project [...]"
Personalised reminders (*n* = 16)	**Suggestions**	8	8	7	"I found it convenient to receive the reminders, both as an alert signal and as a sign of the importance of participation [...]"
Behavioural feedback (*n* = 16)	**Suggestions**	6	10	6	"No. They were precise and punctual."
Whole intervention (*n* = 28)	**Most useful aspect**	15	13	/	"Filling in the diary every time I took a medication helped me remember to take the medications themselves." "The reminders." "The diary are very useful."
Critics/ negative aspects (*n* = 32)	**Problematic/ unhelpful aspects**	18	14	11	"Difficulties in completing the diaries." "The lack of in-person meetings [...]"
	Limitations	14	18	6	"Only computer-based questionnaires; talking with a doctor would be helpful." "Maybe going over the side effects again."

4.2.4 Discussion

The study presented in this section provides a valuable foundation for further exploring medication adherence in the mBC clinical population. The insights gained from the collected data are discussed in detail below.

A central objective of the study was to describe adherence patterns, treatment-related side effects, and relevant psychological variables in patients with mBC. Although these findings must be interpreted cautiously given the small sample, the high adherence observed is nevertheless noteworthy. This pattern is not entirely unexpected: this patient population differ meaningfully from those with early-stage disease, where

extensive evidence documents substantial non-adherence, and, as noted in the introduction, the literature on adherence in mBC remains limited and mixed. These considerations warrant a careful examination of possible explanations for the comparatively higher adherence in this subgroup. The data gathered here provide a useful starting point for that analysis and for generating hypotheses to be tested in future work.

It is important to keep in mind that medication-taking behaviour arises from a complex interplay of factors and cannot be reduced to a single cause (Gast & Mathes, 2019; Moon et al., 2017; Todd et al., 2024; World Health Organization, 2003). Accordingly, the explanations discussed below should be regarded as potential contributors to the high adherence observed, though unlikely on their own to fully account for it.

One plausible explanation is offered by the NCF. This framework highlights how patients' beliefs and representations of their medicines play a central role in shaping adherence behaviours, a premise that has been consistently supported across diverse clinical populations (Foot et al., 2016; Horne et al., 2013). A key hypothesis deriving from this model is that the more patients perceive their treatment as necessary, the more likely they are to adhere. If this is the case, we should expect that early-stage BC patients, among whom non-adherence is widely documented (Murphy et al., 2012; Yussof et al., 2022), would report lower necessity scores on the BMQ compared with metastatic patients, and that non-adherent individuals would show comparatively lower necessity scores than adherent ones. Evidence supporting the latter hypothesis comes from Grunfeld et al., who reported lower necessity scores among non-adherent patients (median = 11; n = 13) compared with adherent ones (median = 15; n = 97) (Grunfeld et al., 2005). Additional confirmation is offered by a meta-analysis showing a positive association between adherence and necessity beliefs across several conditions, including BC (Foot et al., 2016). The findings of the present study appear to support the former hypothesis: our sample obtained higher necessity scores (mean = 21.6; median = 22; SD = 2.9) than the 153 women with early-stage BC in Corter et al.'s study (mean = 13.7; SD = 4.5) (Corter et al., 2013), as well as both the adherent and non-adherent groups in Grunfeld et al. (Grunfeld et al., 2005). Thus, although preliminary, these results reinforce the relevance of medication beliefs in explaining medication-taking behaviour in BC. The observed differences between early-stage and metastatic patients can, at least in part, be explained by the perceptions of treatment necessity. Some early-stage patients, who often experience a sense of being "cured" after initial treatments, may find it difficult to justify continued therapy, particularly given side effects and the absence of active symptoms. In contrast, patients with mBC

are more likely to perceive their treatment as a crucial opportunity to prolong or preserve life.

Another assumption derived from the NCF is that patients implicitly weigh the perceived necessity of their treatment against the concerns and burdens associated with it. The necessity-concerns differential capture this balance, and higher scores have been associated with greater adherence (Foot et al., 2016). Our findings align with this notion, showing relatively high differentials in the sample, with a mean of 6.5 and a median of 7 (SD = 5.2).

Another possible explanation for the high adherence observed lies in the method adopted to measure it, namely the daily medication diary. This tool was chosen to ensure a precise recording of medication-taking behaviour, avoiding reliance on retrospective recall as in standard self-report measures, where patients are asked to remember whether they had taken their medicines over the previous weeks. To minimise recall bias, participants were instructed to update the diary on a daily basis, indicating for each day whether doses were taken or missed, and specifying the number of pills skipped (K. K. Shah et al., 2023). This procedure allowed adherence to be quantified as the proportion of prescribed doses actually taken. At the same time, the use of the diary itself may have influenced behaviour, functioning as a potential BCT (Santoleri et al., 2019). In particular, it can be framed within the technique of *self-monitoring of behaviour* as described in the BCTT and BCTO (Marques et al., 2023; Michie et al., 2013). However, given that one of the aims of this study was precisely to support patients in maintaining their medication-taking behaviour, and considering that the limited sample size drawn from a single hospital could in any case only provide preliminary and non-generalisable insights into adherence, the potential risk of inflating adherence estimates towards optimal levels was deemed acceptable. The value of the diary as a BCT was further supported by participants' comments in the open-ended questions of the satisfaction and perceived utility questionnaire. Four participants explicitly mentioned the diary as helpful for supporting adherence, with three of them identifying it as the most useful component of the intervention. One participant noted that the diary was particularly useful in fostering awareness of the importance of taking the medication, while another remarked that it helped them remember to take their doses. Although these accounts come from a limited number of participants, they nonetheless provide valuable insights into how the diary may be experienced in practice.

Another "unspecific" aspect of the study that may have influenced participants' adherence, not tied to a specific intervention component but rather to the very fact of participating, emerged from the interactions with the researcher required by the study procedures. Meeting patients in person at the beginning of the study, offering support

when needed in carrying out procedures, or contacting them to provide reminders, was in some cases sufficient for participants to feel supported and listened to, and to perceive genuine interest and engagement in their cancer care journey. This point was also reflected in the satisfaction and perceived utility questionnaire, where four participants identified such elements as the most valuable part of the intervention. One participant, for example, observed: "I believe that establishing an ongoing relationship gives us reassurance that we are being taken into account, not only as patients but also as people, and makes us feel listened to." Again, although these views come from a small number of respondents, they nonetheless highlight the potential significance of personal contact and the role that it might play in shaping medication-taking behaviour.

A further factor that may help explain the high adherence observed is volunteer bias. This bias arises when individuals who agree to participate in a study differ systematically from the broader general population, thereby limiting the representativeness and generalisability of the findings. In this context, it is reasonable to hypothesise that patients who consented to take part in the trial may have been, on average, more inclined to follow their HCPs' prescriptions. The likelihood of such bias increases with higher refusal rates (Boughner, 2010). Given that in our study the refusal rate was relatively high (61.4%), this possibility should be carefully considered.

Finally, although the medication diary is a practical and adaptable tool, it nonetheless remains a form of self-report and is therefore vulnerable to social desirability bias. This bias may arise from the natural inclination to provide responses that appear more acceptable (S.Lewis-Beck et al., 2004), which in this context could translate into portraying oneself as more adherent than was actually the case. For this reason, it has been suggested that self-report measures may overestimate adherence (Osterberg & Blaschke, 2005). To mitigate this risk, researchers introduced the study by emphasising the common nature of non-adherence, with the aim of normalising it, and by fostering a relational climate grounded in trust and non-judgement. Despite these efforts, the possibility remains that social desirability may have influenced the adherence reported by some participants.

With regard to side effects and psychological variables, the present study's findings were not surprising; rather, the data corroborate the already well-documented spectrum of side effects associated with oral anticancer therapies, as well as the prevalence of anxiety and depressive symptoms among patients with mBC. The most frequently reported types of side effects were constitutional/systemic symptoms (e.g., fatigue, headache, general discomfort), experienced at least once by 16 participants

(59.3%), gastrointestinal symptoms (e.g., nausea, diarrhoea, constipation; *n* = 13, 48.1%), musculoskeletal/osteoarticular pain and symptoms (e.g., joint pain, bone pain; *n* = 10, 37%), and cutaneous and dermatological symptoms (e.g., cracks on hands and feet, dry skin, skin rash; *n* = 7; 25.9%). These patterns are consistent with the treatments received by the sample: fatigue and nausea—the most commonly reported items within the constitutional/systemic and gastrointestinal categories, respectively (see Appendix 10)—are typical adverse effects of targeted agents, particularly cyclin-dependent kinase 4/6 inhibitors (LeVee et al., 2025), which were used by more than half of participants (56.3%). Joint pain, frequently reported here, is also a recognised consequence of aromatase inhibitors (often termed aromatase inhibitor-induced arthralgia) (Beckwée et al., 2017); aromatase inhibitors were taken by over one third of the sample (34.4%), in combination with targeted therapy, which aligns with the 37% reporting at least one musculoskeletal/osteoarticular symptom. Oral chemotherapy (43.8% of the sample), particularly capecitabine alone or combined with vinorelbine and cyclophosphamide, is likewise associated with nausea, vomiting, and diarrhoea (Montagna et al., 2017; Nhean et al., 2021; Valerio et al., 2021), and participants indeed reported these effects, especially nausea.

Considering intensity, mean scores for side effect categories were generally in the moderate range (from 5.0 to 6.7), with the exception of sensory and respiratory symptoms (means 7.7 and 8.1, respectively). These two categories together accounted for only 0.4% of all adverse events, so their influence on the overall findings is minimal. Given that side effects are often cited as a key driver of medication non-adherence (Todd et al., 2024; Yussof et al., 2022), another plausible explanation for the high adherence observed in this sample is that, although side effects were present and sometimes bothersome, their predominantly moderate intensity, combined with the strong perceived necessity of treatment, was not sufficient to compromise adherence.

With regard to anxiety, mean STAI-Y scores (ranging from 41.8 to 44.4) suggest a generally mild level of symptomatology. These values are comparable to, or slightly lower than, those reported in previous studies with BC patients (Mazzocco et al., 2023) and with individuals with mBC (Marcondes et al., 2024). One possible explanation for these findings is that, on average, participants had received their initial BC diagnosis eight years prior to recruitment, which may have allowed them time to develop coping strategies and adapt to their condition. Moreover, the continuation of treatment may also have fostered a sense of control over the illness and nurtured hope for the future, which could in turn have mitigated feelings of anxiety. Naturally, these are only exploratory considerations that cannot be confirmed with the present data, but should be investigated in specifically designed studies.

With regard to depressive symptoms, BDI-II scores (means 10.3—12.7) generally fell within the minimal range. Nonetheless, despite these low mean values for both anxiety and depressive symptoms, a small but relevant subset of participants reported clinically significant distress: two participants reached the threshold for severe depressive symptoms and three for severe anxiety. When including those whose score fell in the moderate range, the proportion of participants experiencing at least moderate symptoms ranged between 23% and 40% for anxiety and between 8% and 25% for depressive symptoms across the study time-points. Taken together, these results underscore the importance of routine screening for psychological distress in patients with mBC, alongside timely access to psychological support and early intervention when indicated.

Concerning the assessment of quality of life dimensions as measured with the EORTC-QLQ-C30 and with the BC-specific module BR23, our findings suggest a mixed picture. Our sample reported better preservation of daily activities and greater emotional well-being compared with the available reference values for patients with mBC (Scott et al., 2008), and fewer physical complaints in some domains, such as pain, appetite loss, breast and arm symptoms, but greater psychosocial distress related to body image and hair loss. However, the overall quality of life was comparable to that of the reference population.

The present study also pursued the objective of assessing the feasibility, patient satisfaction, and perceived usefulness of three intervention components, namely, educational material, personalised reminders, and behavioural feedback, with the aim of informing whether, and in what form, they might be tested in a fully powered optimisation study or a randomised controlled trial. The adoption of a full factorial design made it possible to examine every possible combination of the three components, thereby confirming the feasibility of this approach. The study procedures and delivery of the intervention components were implemented smoothly, without major obstacles and at minimal cost, the only expense being the premium feature of the WhatsApp extension Blueticks, which enabled the scheduling and sending of personalised reminders. Results from the satisfaction and perceived usefulness questionnaire indicate that most participants found the intervention helpful and were satisfied with its features. Nevertheless, some participants expressed doubts regarding the usefulness of the medication diary, as indicated by ratings of 1 or 2 on the 5-point Likert scale (five respondents out of 25 for this item; see Appendix 12). One participant additionally reported dissatisfaction with the educational material, although they acknowledged not having read the material. While this individual rated also the

overall intervention as neither useful nor satisfactory, they did express positive judgement regarding the behavioural feedback.

These observations highlight the need for a personalised approach to interventions, as not all patients with mBC have the same preferences or informational needs. Although assignment to intervention components was random by study design, it is reasonable to hypothesise that allowing patients to choose the components they receive could further minimise dissatisfaction, even among the few participants who expressed it.

In conclusion, the proposed intervention proved to be feasible, inexpensive, and generally perceived as supportive of adherence by those who received it. However, the very high adherence rates observed in the sample prevented us from detecting even preliminary signals of effectiveness, which could only be addressed in specifically designed, adequately powered studies. This raises a legitimate question: is it worthwhile to further test these three components in this specific population? A potentially more suitable next step may instead be to conduct a larger, low-burden study with the primary objective of estimating the prevalence and magnitude of non-adherence to oral therapies in mBC. Keeping procedures as simple as possible would help reduce refusal rates and yield a more realistic picture of this group's needs. Depending on those findings, one could either proceed with a fully powered optimisation trial in mBC (if non-adherence proves substantial) or, alternatively, redirect effort toward early-stage BC, where non-adherence is more prevalent according to the literature. In that case, only the educational component would require content adaptation; reminders and feedback are likely transferable across disease stage with minimal tailoring.

Study limitations

This pilot study presents some noteworthy limitations. First, the small sample size and single-centre recruitment limit the generalisability of the findings: the results should be seen as a preliminary glimpse of adherence, side effects, and psychological variables in this specific group rather than as representative of the broader mBC population. In addition, the unexpectedly high adherence observed further restricted the scope of the analysis, making it impossible to draw even exploratory suggestions about the potential effectiveness of the intervention components on the primary outcome of interest, namely adherence to oral therapies. For the same reason, it was not feasible to investigate their possible impact on psychological variables or quality of life.

Second, adherence was assessed exclusively via a daily medication diary, a self-report method that is vulnerable to social desirability, thus presenting the risk of overestimating adherence. We chose the diary to minimise recall bias, and we

attempted to mitigate desirability effects by normalising non-adherence during enrolment and fostering a non-judgemental relationship between the researchers and participants. Nevertheless, self-report remains an imperfect measure and may have inflated adherence estimates for some participants.

Third, the study suffered from a relatively high refusal rate, which raises the possibility of volunteer bias: people who agreed to participate may differ systematically from those who declined, for example being more motivated in following the HCPs' instructions. This further constrains the external validity of the results.

Finally, the fact that treatment-related side effects were self-reported by participants may raise concerns about the accuracy of the data. As some participants noted in the open-ended questions of the final questionnaire, it was at times challenging to distinguish symptoms attributable to the treatment from those related to the disease itself or to other concurrent conditions.

Despite these limitations, the study offers useful preliminary information and practical lessons for future work. The issue of non-adherence among mBC patients has received only limited attention from the scientific community: our study represents a valuable starting point providing several interesting directions for future scientific endeavour. If this lines of inquiry will be pursued, this might lead to further deepening in the understanding of medication adherence and eventually meaningful improvements in the care journey of this clinical population.

Clinical implications

The present pilot study provides important insights into the phenomenon of non-adherence in general and, more specifically, within the mBC clinical population. Data obtained through the administration of the BMQ appear to further support the central hypothesis advanced by the proponents of the NCF, namely that medication-taking behaviour can, at least in part, be explained by patients' evaluation of the perceived necessity of treatment weighed against their concerns. This has implications both at the theoretical level, by deepening our understanding of the phenomenon examined in this doctoral thesis, and at the clinical level, where a tool as straightforward as the BMQ can be employed as an initial screening instrument to identify patients at higher risk of non-adherence. Moreover, the principles underlying the NCF can guide the development of tailored interventions aimed at addressing patients' beliefs about medicines, by clarifying the necessity of treatment and directly addressing their concerns.

A further clinically relevant finding relates to the presence of moderate to severe psychological distress in a minority, yet substantial, proportion of participants: between 23% and 40% reported moderate to severe anxiety, and between 8% and

25% moderate to severe depressive symptoms. These results highlight the importance of implementing systematic screening for psychological distress in patients with mBC, with the aim of providing timely psychological support when most needed. Such an approach would foster a more integrated model of cancer care, where treatment extends beyond the medical dimension to include patients' psychological, emotional, and social experiences.

Finally, regarding the intervention itself, this pilot study demonstrated the feasibility and the perceived usefulness of a low-cost, multi-component programme specifically designed for patients with mBC. The components were easy to deliver, acceptable to participants, and could be readily tested in larger populations. With minor adaptations, they could also be applied to other clinical groups. While this study should be regarded more as a starting point than a conclusion, it nonetheless contributes meaningfully to the field, offering theoretical and practical insights that can inform future research, clinical practice, and the design of interventions to address the challenge of non-adherence.

Conclusions

The pilot study described in this chapter demonstrated the feasibility of a multi-component intervention to support medication adherence among patients with mBC. The three components tested, educational material, personalised reminders, and behavioural feedback, were generally perceived as useful by participants who received them, suggesting that they could be evaluated in a larger optimisation trial to assess their effectiveness, both individually and in various combinations, within a fully-powered factorial design. However, adherence rates in the present sample were higher than anticipated. For this reason, a study involving a larger cohort, specifically aimed at establishing the prevalence and extent of non-adherence within the mBC population, may represent a necessary intermediate step before proceeding to the optimisation trial.

Participants' beliefs about medicines, as conceptualised within the NCF, may partly account for the high adherence observed, as they tended to view their treatment as highly necessary. In addition, a substantial proportion of participants reported moderate to severe psychological distress, underscoring an unmet need for accessible psychological support in this population.

In conclusion, this pilot study offers meaningful insights into the phenomenon of medication non-adherence among patients with mBC. These insights warrant further exploration in order to deepen our understanding of the prevalence and underlying mechanisms of non-adherence, and to inform the development and implementation of

targeted strategies to support those patients who may encounter difficulties in maintaining adherence to their prescribed therapies.

5. General discussion

This final chapter provides an overall synthesis of the work conducted, followed by a discussion of the main conclusions that can be drawn, additional reflections, and the closing remarks.

This doctoral thesis investigated medication non-adherence in patients with BC. We began with a comprehensive overview of the topic, clarifying key definitions of non-adherence and discussing existing evidence on its determinants and on interventions designed to support adherence. Promising directions, such as approaches enabled by advances in AI, were also discussed. The clinical context of BC was then outlined, covering its prevalence, main subtypes, and the treatments most commonly used.
Chapter 2 set out the theoretical and methodological foundations underpinning the scientific investigation of medication adherence. After introducing the field of health psychology, we reviewed several models of health behaviour developed over recent decades. We then described the BCTT and the BCTO as frameworks that help identify the active elements of behaviour change interventions. The chapter closed by presenting the factorial design as a particularly suitable approach for optimising and evaluating multi-component interventions, such as those aimed at improving patients' adherence.
With these foundations established, the thesis proceeded to present the reviews and original studies that form its core.

5.1 Summary of findings

Three literature reviews were carried out to deepen our understanding of non-adherence in BC and to synthesise the extensive evidence available on the topic.
Study 1 (Pezzolato, Marzorati, et al., 2023) was a systematic review of interventions aimed at improving medication adherence in patients with BC. By synthesising 36 primary studies, it mapped the current state of the field and highlighted clear patterns: most interventions were delivered via eHealth, and research has focused predominantly on early-stage BC and on endocrine therapy, revealing important gaps for future work. A thorough content analysis using the BCTT identified the BCTs most commonly employed—information about health consequences, social support, prompts/cues, and problem solving—and pointed to the techniques most frequently present in effective interventions—prompts/cues, feedback on behaviour, and information about health consequences. Moreover, the considerable heterogeneity in both contents and outcomes, combined with the relatively low rate of success (only 35% of studies reported statistically significant improvements in adherence), further

reinforced the view of non-adherence as a complex and multifaceted phenomenon. These findings suggest that it is unlikely to be effectively addressed by standardised, one-size-fits-all approaches.

Study 2 (Pezzolato, Spada, et al., 2023) was a scoping review examining the use of predictive models to identify non-adherence among BC patients. Such models may offer a way to allocate limited healthcare resources more effectively, potentially ensuring that adherence-supporting interventions are directed to those at higher risk. The review identified six models, based on different methodological approaches, including multivariate binomial and logistic regression analyses, behavioural feedback-based decisional frameworks, and Cox proportional hazards models. Across these studies, a range of demographic, treatment-related, behavioural, and psychological variables were tested as potential predictors. Factors such as younger age (or, in one case, both younger and older age groups), lower body mass index, taxane-based chemotherapy, and pain symptoms were associated with poorer adherence, alongside psychological variables including low perceived risk, limited concern about recurrence, depression, anxiety, and poor quality of life. Yet, despite this variety of predictors, one third of the models showed limited predictive accuracy, pointing to the need for more rigorous validation and calibration before these tools can be meaningfully applied in clinical practice. In this sense, the review not only summarised current approaches but also underscored their limitations, drawing attention to the persistent implementation gap in the field.

Study 3 (Pezzolato et al., 2025) built on the themes introduced in Study 2 by focusing specifically on the role of AI in predicting and supporting adherence. This systematic review identified seven studies: six presented ML-based predictive models of non-adherence, while one described an AI-powered chatbot with a reminder function. The analysis offered an updated overview of the field, while also highlighting persistent shortcoming. Across predictive studies, methodological weaknesses such as lack of external validation, absence of calibration, and failure to address implementation limited both credibility and clinical applicability. Similarly, the intervention study raised concerns due to incomplete reporting, potential confounders, unclear reporting of the study's findings, and low engagement with the reminder function, underscoring the need for more rigorous evaluation in larger samples. Beyond this limitations, the review emphasised the importance of ensuring that AI tools are not only accurate but also actionable and safe in real-world practice. Ethical and safety issues, including patient privacy, data security, model transparency, and algorithmic bias, were identified as crucial considerations to be addressed in future developments.

After having delved deep into the scientific literature on the topic through these three reviews, two original studies were presented in Chapter 4. These studies also marked a shift in the focus specifically toward individuals with mBC.

Study 4 (Masiero et al., 2024) was a qualitative investigation involving four focus groups with 19 mBC patients, aimed at exploring barriers and facilitators of adherence, as well as perspectives on digital tools. Side effects emerged as the most frequently cited obstacle, highlighting their central role in shaping medication-taking behaviour. The patient-clinician relationship appeared as a dual-edged factor: discontinuity and poor communication were described as barriers, whereas empathy and attentiveness were viewed as facilitators. Regarding digital health, participants expressed scepticism about clinical usefulness, yet sentiment analysis revealed positive associations when such tools enabled peer connection, shared experiences, or timely professional guidance. These findings suggest that eHealth solutions designed to combine interpersonal support with personalised, reliable content may be particularly effective for this population.

Finally, **Study 5** was a pilot optimisation trial testing the feasibility, perceived usefulness, and satisfaction with a multi-component intervention to support adherence in mBC. The intervention included three elements, educational material, personalised reminders, and behavioural feedback, combined in a full factorial design. Overall, it proved feasible and well received by participants, who considered it potentially useful. However, adherence rates were unexpectedly high, limiting the possibility of drawing even exploratory suggestions about effectiveness. Several explanations were considered, including strong beliefs in treatment necessity, the possible influence of the medication diary itself as a behavioural change tool, and non-specific relational factors linked to trial participation. Despite this limitation, the study generated valuable insights into patients' beliefs, side effects, and psychological distress, while also confirming the feasibility of the intervention. The findings highlight the necessity of larger trials to clarify adherence prevalence and to assess the intervention's true potential.

From these five studies, the following principal takeaways can be drawn:

- Medication adherence is a multifactorial phenomenon shaped by diverse determinants, and many interventions designed to improve it prove only partially effective. Among BC patients, interventions incorporating prompts/cues and behavioural feedback appeared promising, suggesting that these BCTs may be particularly relevant for this population;

- Predictive modelling of adherence remains challenging, with most attempts hampered either by limited predictive accuracy or by insufficient validation and implementation strategies;
- ML-based predictive models share these limitations: their computational power is not sufficient without large, high-quality datasets and clear strategies for clinical implementation. In addition, their development and application must carefully address ethical and safety issues, including privacy, transparency, and potential bias;
- For patients with mBC, treatment side effects represent the most significant barrier to adherence, while the patient-clinician relationship emerged as pivotal: poor communication and discontinuity in care act as obstacles, whereas empathy and attentiveness facilitate adherence;
- Digital tools are increasingly used to support adherence. While patients with mBC expressed scepticism about their clinical utility, they showed openness when these tools enabled timely communication with HCPs and fostered a peer support and a sense of community;
- Patients with mBC may demonstrate higher adherence than those in early-stages of the disease, partly due to their stronger perception of treatment necessity;
- Identifying patients with mBC who experience moderate to severe psychological distress or difficulties with adherence is crucial to provide timely support and tailored interventions;
- A multi-component intervention combining educational material, reminders, and feedback proved feasible, low-cost, and well-received by patients with mBC.

5.2 Additional considerations and future directions

The guiding thread of this doctoral thesis is built around a twofold and highly practical question: (1) how can patients with BC, and especially those living with metastatic disease, be supported in remaining adherent to their oral therapies? And (2) given the constraints and limited resources of healthcare systems, how can we identify those individuals most in need of targeted interventions or additional support?

The path taken in this work represents only one of the possible directions toward more effective answers. In addressing the first question, attention was placed on "individual-level" interventions, deliberately leaving aside system-level or provider-level approaches. To tackle the second question, predictive models were examined, given their potential to serve as screening tools for identifying patients at higher risk of non-adherence. By pursuing these avenues, other possible strategies were

necessarily set aside, approaches that have been extensively investigated by other research groups.

Among these, the work carried out at the Centre for Adherence Research and Education (CARE) at the King's College London represents a particularly interesting and complementary perspective. Their approach provides a straightforward response to the second of our guiding questions (how to identify individuals most in need of additional support): by simply asking patients, provided this is done in an appropriate way. CARE researchers recognised that HCPs are best positioned to initiate respectful and constructive conversations about adherence. At the same time, they acknowledged the risk that patients, when asked bluntly by a physician or nurse whether they take their medication as prescribed, may provide socially desirable answers, downplaying or denying adherence difficulties (Engel et al., 2017).

To address this, they developed *Making Medicines Work For You* (©MMWFY) a brief screener co-designed with patients and clinicians to facilitate open, non-judgemental discussions on medication use. The tool is intended to highlight potential barriers to adherence in a way that normalises difficulties and fosters honest communication. Pilot testing of ©MMWFY among patients with type 2 diabetes showed promising results: the screener proved to be a sensitive indicator of non-adherence and its determinants, correlating strongly with established measures such as the Morisky Medication Adherence Scale-8 and the BMQ (Weinman et al., 2019).

CARE also provide training for HCPs on how to administer the screener and integrate it effectively into routine consultations. Beyond learning how to introduce the tool and adopt a collaborative, non-judgmental stance, HCPs are instructed in a set of adherence support strategies tailored to the barriers patients report. For example, if a patient indicates "I sometimes forget to use the medicine(s)," the provider is trained to apply the BCT of *action planning*, helping the patient to specify when, where, and with whom they will take their daily medication, and to link this activity to a consistent daily cue.

This approach illustrates a virtuous provider-level intervention: by equipping HCPs with both a tool to open the conversation and practical techniques to address identified barriers, each consultation can directly support adherence. Moreover, as trained providers apply these skills with their patients, the potential impact of the intervention becomes amplified across routine clinical practice.

An interesting future direction to strengthen adherence support for cancer patients could be to apply this approach within an oncological hospital and research centre such as IEO. Translating the ©MMWFY into Italian and training HCPs in its use would enable patients to discuss adherence issues directly with their clinicians in a

supportive, non-judgemental manner. A pilot study assessing the feasibility and acceptability of this approach in our setting would represent the most advisable next step.

In parallel, future research should also pursue the avenues outlined in the discussion of Study 5. Specifically, conducting a larger, low-burden study aimed at estimating the prevalence and magnitude of non-adherence to oral therapies in mBC appears crucial. Depending on its outcomes, subsequent efforts could involve either a fully powered optimisation trial in the mBC population or, alternatively, a shift in focus toward early-stage BC, where evidence of non-adherence is currently stronger.

5.3 Conclusions

This doctoral thesis provides a comprehensive examination of the problem of medication non-adherence among BC patients. Beyond synthesising and critically discussing existing knowledge through the introductory chapters and three literature reviews, it advances the field with two original studies focusing on mBC patients. The findings contribute to a deeper understanding of adherence, its predictors, and the interventions designed to address it, while also generating new evidence on the mBC population, historically less studied than those in earlier stages. Taken together, the findings from the thesis, as summarised in this final chapter, highlight the need for tailored, patient-centred strategies that integrate clinical, psychological, and relational dimensions, thereby paving the way for future research and practice to improve adherence and enhance the well-being of patients living with cancer.

Appendix 1. *Complete search strings for Studies 1, 2, and 3.*

The complete search strings used for each of the literature reviews included in this doctoral thesis are reported below. For clarity, only the Scopus format is presented. The corresponding strings for the other databases are identical in content, with differences limited to database-specific formatting of filters.

Study 1:

((TITLE-ABS (intervention* OR study OR trial)) AND (TITLE-ABS ("endocrine therapy" OR "hormon* therapy" OR "oral antineoplastic agent*" OR "endocrine treatment" OR "hormon* treatment" OR "aromatase inhibitor" OR "oral chemotherapy" OR "oral therapy" OR "targeted therapy" OR "oral treatment" OR "oral anticancer agent*")) AND (TITLE-ABS (cancer OR tumor OR neoplasm)) AND (TITLE-ABS (compliance OR adherence))) AND breast

Study 2:

(breast cancer) AND ((TITLE-ABS (predictive model OR prediction model OR prognostic model OR prediction tool OR predictive tool OR prognostic tool)) AND ((TITLE-ABS (quality of life OR depression OR anxiety OR distress OR adherence OR compliance OR psychological OR psychosocial))

Study 3:

(TITLE-ABS-KEY (adherence) OR TITLE-ABS-KEY (compliance) OR TITLE-ABS-KEY (nonadherence) OR TITLE-ABS-KEY (non-adherence) OR TITLE-ABS-KEY (noncompliance) OR TITLE-ABS-KEY (non-compliance)) AND (TITLE-ABS-KEY ("natural language processing") OR TITLE-ABS-KEY (NLP) OR TITLE-ABS-KEY ("neural networks") OR TITLE-ABS-KEY ("artificial intelligence") OR TITLE-ABS-KEY (AI) OR TITLE-ABS-KEY ("machine learning") OR TITLE-ABS-KEY ("deep learning") OR TITLE-ABS-KEY ("large language model") OR TITLE-ABS-KEY (LLM) OR TITLE-ABS-KEY (robotics)) AND (TITLE-ABS-KEY ("breast cancer"))

Appendix 2. *BCTs identified in each intervention included in Study 1 using the BCTT.*

Author	Year	1.1	1.2	1.4	2.1	2.2	2.3	3.1	3.3	4.1	5.1	5.2	6.1	6.2	7.1	7.3	8.1	9.1	9.2	10.4	11.2	12.5	12.6	13.2	13.4	14.8
Arch	2022		X								X				X						X				X	
Bhandari	2019				X																	X				
Bluethmann	2021										X															
Chalela	2018		X				X	X		X	X		X		X			X		X						
Ell	2009		X					X	X		X									X						
Ferraris	2020																									
Getachew	2022				X			X			X				X			X								
Graetz	2018					X	X																			
Hadji	2013							X			X				X						X	X				
Heisig	2015										X							X								
Hershman	2020							X			X				X			X								
Jacob	2015										X															
Jacobs	2022		X		X			X			X							X			X		X	X		
Komatsu	2020		X					X			X							X								
Krok-Schoen	2019		X			X	X				X				X					X						
Lee	2020					X									X											
Mamguem Kamga	2020		X								X				X			X								
Markopoulos	2015										X	X									X					
Meguerditchian	2016				X	X																				
Moon	2019	X	X	X				X			X	X		X	X									X		
Mougalian	2017		X			X	X	X		X					X											
Myers	2022																						X			
Paladino (1)	2019						X																			
Paladino (2)†						X	X	X																		
Park	2021					X		X							X							X				
Ream (1)	2021							X																X		
Ream (2)†								X													X		X			
Riis	2020							X																		
Sanft	2021		X								X															
Shelby	2019	X	X	X		X				X	X		X		X	X	X	X	X	X	X		X	X		X
Smith	2022		X					X										X			X				X	
Tan	2020			X											X											
Von Blanckenburg	2013		X					X			X								X				X	X		
Wagner	2016							X										X								
Yanez	2022							X			X										X		X			
Yu	2021						X								X											
Yu	2012										X															
Ziller (1)	2013							X			X				X											
Ziller (2)†			X					X			X				X			X								

1.1 = Goal setting (behaviour); 1.2 = Problem solving; 1.4 = Action planning; 2.1 = Monitoring of behaviour by others without feedback; 2.2 = Feedback on behaviour; 2.3 = Self-monitoring of behaviour; 3.1 = Social support (unspecified); 3.3 = Social support (emotional); 4.1 = Instruction on how to perform the behaviour; 5.1 = Information about health consequences; 5.2 = Salience of consequences; 6.1 = Demonstration of the behaviour; 6.2 = Social comparison; 7.1 = Prompts/cues; 7.3 = Reduce prompts/cues; 8.1 = Behavioural practice/rehearsal; 9.1 = Credible source; 9.2 = Pros and cons; 10.4 = Social reward; 11.2 = Reduce negative emotions; 12.5 = Adding objects to the environment; 12.6 = Body changes; 13.2 = Framing/reframing; 14.8 = Reward alternative behaviour;
† = Studies in which more then one intervention is proposed are reported twice.

Adapted from Pezzolato et al., Psycho-Oncology, 2023.

Appendix 3. *Study 4, focus group discussion guide.*

Introduction

- *Introduction of the researchers facilitating the discussion;*
- *Overview of the Pfizer project, "Enhancing Therapy Adherence Among Metastatic Breast Cancer Patients," including its overarching aims;*
- *Briefly introduction to the topic of medication adherence, emphasising that many patients find it challenging to take their medication consistently, with the aim of normalising these difficulties and avoiding any sense of judgement;*
- *Presentation of the goals of the focus groups: to gain insights into participants' perspectives and experiences related to treatment adherence, to explore perceived barriers and facilitator, and ultimately to understand how best to support them;*

AREA 1: Personal clinical experience and care trajectory

- *Round of introductions, during which participants are invited to share their clinical history and care trajectory;*

AREA 2: Barriers to maintaining adherence to oral anticancer therapies

- *Some patients find it difficult to take their medication consistently without skipping doses. In your experience, what barriers, obstacles, or difficulties have you encountered in maintaining regular medication adherence?*
- *Based on what you have observed or heard from others, what barriers, obstacles, or difficulties do you think other patients with your condition face?*
- *More broadly, why do you think some patients find it difficult to adhere to their treatment? What barriers or challenges do you imagine others with your condition might experience?*

AREA 3: Resources and facilitators supporting treatment adherence

- *In your experience, what resources or facilitators help you take your medication as prescribed?*
- *Do you use any particular strategies to manage you medication-taking? Are there any approaches you would like to share with the group that might be helpful to others?*
- *Thinking about other patients with a condition similar to yours, what resources or facilitators do you know they use to support their medication-taking?*
- *More broadly, what resources or facilitators do you think might help other patients manage their medication more effectively?*

- *From your perspective, what could we do to better support you, or other patients, with medication adherence?*

AREA 4: Views and attitudes toward digital technologies for adherence support

- *Would you consider using a digital tool to support your adherence? If yes, which features or characteristics would you find helpful? What kind of information, if any, would you want it to include?*

- *Do you think that such a tool could support you in staying adherent to your medication? And do you think it could help other patients?*

- *Is there anything else that you think could be useful to you, or to other patients, in a tool of this kind that we have not mentioned?*

Closing remarks

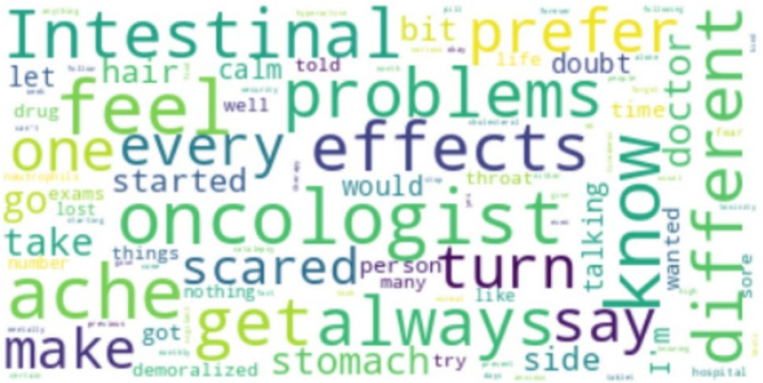
- *Providing information about the possibility of receiving psychological support at the Institute, if needed;*

- *Sharing the researchers' contact details, should any questions or doubts about the project, adherence, or any related topic arise after the meeting;*

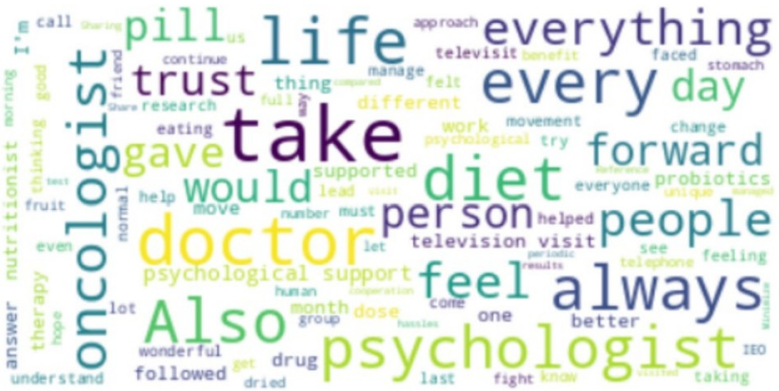
- *Acknowledging the importance of participants' contributions in helping us better understand medication adherence and improve support for patients;*

- *Thanking everyone for their contributions, time, and engagement, and offering final greetings.*

Appendix 4. *Word cloud illustrating key terms associated with Theme 2, 3, and 4.*



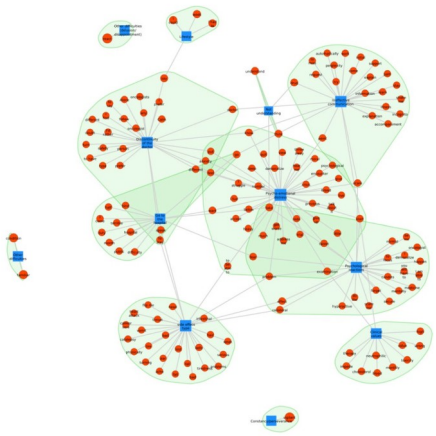
A. Word cloud illustrating key terms associated with Theme 2: Barriers to adherence. Adapted from Masiero et al., Supportive Care in Cancer, 2024.



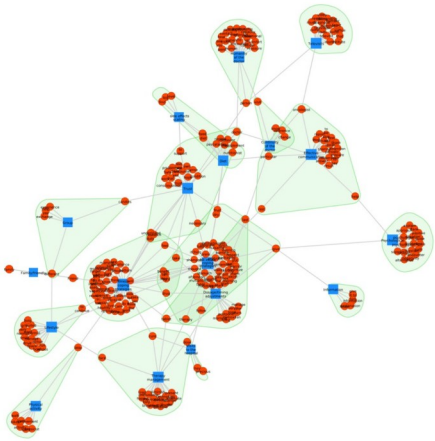
B. Word cloud illustrating key terms associated with Theme 3: Resources supporting adherence.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.

C. Word cloud illustrating key terms associated with Theme 4: Attitudes toward adherence-focused digital tools.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.

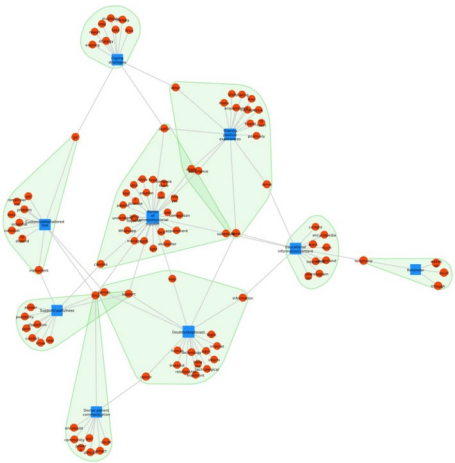
Appendix 5. *Network analysis of Theme 2, 3, and 4, illustrating the main concepts discussed and their interconnections. The blue squares represent the main categories while the red circles represent the key-words.*



A. Network analysis of Theme 2: Barriers to adherence.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.

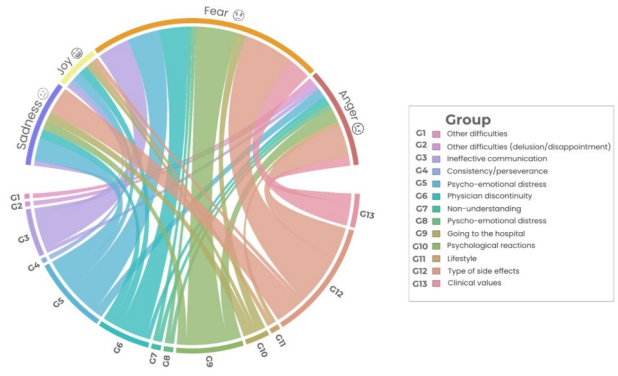


B. Network analysis of Theme 3: Resources supporting adherence.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.

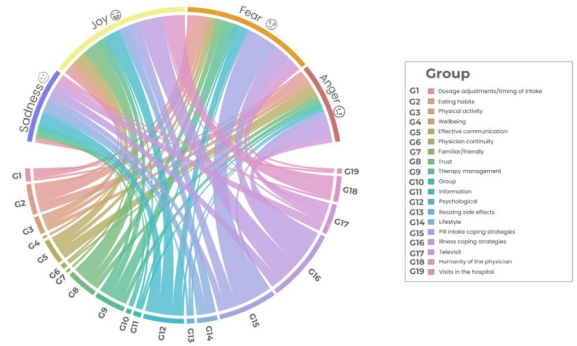


C. Network analysis of Theme 4: Attitudes toward adherence-focused digital tools.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.

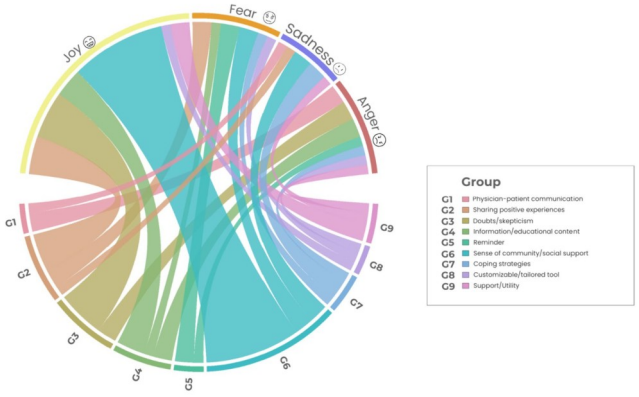
Appendix 6. *Circos plot for Theme 2, 3, and 4, illustrating the relationships between sub-themes and emotions.*



A. Circos plot for Theme 2: Barriers to adherence.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.



B. Circos plot for Theme 3: Resources supporting adherence.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.



C. Circos plot for Theme 4: Attitudes toward adherence-focused digital tools.
Adapted from Masiero et al., Supportive Care in Cancer, 2024.

Appendix 7. Study 5, BCTs identified in each intervention component using the BCTT.

Intervention component		BCTs
Educational material	Section A	*Reduce negative emotions*
	Section B	*Information about health consequences*
	Section C	*Social support, goal setting (behaviour), problem solving, action planning, commitment, self-monitoring of behaviour, information about antecedents, prompts/cues, habit formation, pros and cons, self-incentive, framing/reframing*
	Overall	*Credible source*
Personalised reminders		*Prompts/cues, information about health consequences*
Behavioural feedback		*Feedback on behaviour, information about health consequences, social support, social reward*

Appendix 8. *Full list of personalised reminders and behavioural feedback messages used in Study 5.*

A. Personalised reminders.

1. 🌼 Buongiorno! È tempo di prendere la tua medicina. Ricorda, la tua salute è la tua ricchezza più grande!

2. 🕰️ Ciao! È il momento del tuo farmaco. Non dimenticarlo, ogni piccolo passo conta!

3. 🌷 Ti sei ricordata di prendere il tuo medicinale oggi? È importante per la tua salute!

4. 🌈 Un altro giorno, un altro passo verso il benessere. Non dimenticare di prendere il tuo farmaco.

5. ⏰ È l'ora del tuo farmaco. Ricorda, ogni dose è importante per il tuo percorso di cura.

6. 💌 Un piccolo promemoria: è ora della tua medicina.

7. 🌼 Buongiorno! Non dimenticare di assumere la tua medicina.

8. ⏰ Ciao! Non dimenticare di prendere il tuo farmaco, è importante per la tua salute.

9. 🌼 Buongiorno! Ricorda di assumere le tue medicine per garantire che funzionino nel migliore dei modi.

10. 💊 Ciao! Anche oggi, non dimenticarti di prendere il tuo farmaco. La tua salute viene prima di tutto!

B. Behavioural feedback.

Adherence rate <80%

*Sembra che tu abbia saltato qualche dose dei tuoi farmaci. So che può essere difficile ricordarli sempre o farli diventare parte della tua routine, ma la costanza è davvero importante affinché la tua terapia farmacologica funzioni correttamente. Se ti va di parlare delle difficoltà o degli ostacoli che hai incontrato scrivi a questa mail: **********. Cercheremo di aiutarti a riprendere il "ritmo" del tuo percorso di cura.*

Adherence rate >80%

Ottimo lavoro! La tua costanza nell'assunzione dei farmaci aiuterà davvero a far sì che il tuo farmaco funzioni nel migliore dei modi. Continua così!

Appendix 9. *Study 5, adherence percentage at the four time-points, divided by presence or absence of each of the three interventions.*

Time-point	Educational material				Personalized reminders				Feedback			
	No		Yes		No		Yes		No		Yes	
	N	Adherence (%)	*N*	Adherence (%)	*N*	Adherence (%)	*N*	Adherence (%)	*N*	Adherence (%)	*N*	Adherence (%)
T1 (1 month)	13	99.5	14	98.3	14	99.4	13	98.4	13	98.2	14	99.5
T2 (3 months)	14	99.2	12	98.8	13	99.4	13	98.6	12	98.8	14	99.2
T3 (5 months)	12	99.5	13	98.5	11	99.3	14	98.8	12	98.6	13	99.5
T4 (7 months)	9	99.2	14	98.1	10	98.6	13	98.5	13	98.4	10	98.9

Appendix 10. *Study 5, distribution of adverse events according to specific side effect.*

Side effect categories	Reported side effects	*n*
Gastrointestinal symptoms	Nausea	454
	Gastric disturbances	11
	Abdominal bloating	47
	Diarrhoea	24
	Bowel disturbances	9
	Abdominal colic	41
	Constipation	199
	Vomiting	3
	Frequent bowel movements	28
	Stomach heaviness	24
Constitutional/ systemic symptoms	General discomfort	**8**
	Fatigue	**974**
	Headache	89
	Sleepiness	11
	Chills	1
	Anaemia	21
	Swollen lymph nodes	1
Musculoskeletal/osteoarticular pain and symptoms	Pain	269
	Joint pain	219
	Bone pain	157
	Back pain	91
	Cramps	1
	Joint stiffness	12
	Reduced mobility	154
Cutaneous and dermatological symptoms	Cracks on hands and feet	162
	Dry skin	455

Side effect categories	Reported side effects	*n*
	Skin rash	91
	Itching	124
	Swelling (limbs, face)	7
	Scalp crusts	13
	Hand-foot syndrome	5
Psycho-emotional symptoms	Insomnia	49
	Feelings of emptiness	1
	Mental heaviness	2
	Restlessness	1
	Memory problems	1
Mouth, taste, and smell alterations	Dysphagia	77
	Mouth disorders	10
	Altered taste	4
	Bad breath	1
Symptoms involving nose, throat, and eyes	Dry nose and throat	175
	Conjunctivitis	2
	Eye burning	3
	Watery eyes	4
Aesthetic and metabolic alterations	Hair loss	225
	Excess hair growth	2
	Weight gain	3
Vasomotor and cardiovascular symptoms	Hot flushes	5
	Palpitations	216
Vertigo and dizziness	Dizziness	3
	Vertigo	1
Sensory symptoms	Blurred vision	7
	Vision loss	2

Side effect categories	Reported side effects	*n*
	Hearing loss	1
Respiratory symptoms	Dyspnoea	1
	Cough	10

Appendix 11. *Study 5, participants' responses to the satisfaction and perceived utility questionnaire.*

	Item	*n*	Missing	No suggestions	Answers
Medication diaries (*N* = 32)	**Suggestions**	17	15	10	"I would have created a diary via an app or in digital form. I find it an easier tool to manage than paper sheets." "I had some doubts when describing side effects (for me, only fatigue), especially when they might have also been caused by other factors (occasional illness, flu, etc.)." "Digital format and possibility of a list of possible side effects, as in the package leaflet." "Create an app that allows filling in the diaries directly and that can send them." "I found them well designed and intuitive to understand and complete; for me, they are more than fine as they are. Perhaps if they were slightly larger, it would be possible to write more and go into detail, but maybe a good synthesis is preferable in order to extract the data." "It would be useful to follow all cancer patients by providing them with in-person psychological support." "In my experience, the diaries can be useful for a limited period of no more than two months, just enough to become aware of the need to take the medication. I was not always able to complete them on time."
Educational material (*n* = 16)	**Clarity/ improvement**	5	11	4	"There was a lack of in-person meetings with a psychologist to also explore one's personal psychological state, not only aspects related to the project. While it is important for patients to support research, it would also be helpful to assess their condition in order to help them live more serenely and to find personal coping strategies."
Personalised reminders (*n* = 16)	**Suggestions**	8	8	7	"I found it convenient to receive the reminders, both as an alert signal and as a sign of the importance of participation. As for the daily completion, it is simply a matter of organising it within one's routine." "If it became digital, I would include the reminder option."

	Item	*n*	Missing	No suggestions	Answers
Behavioural feedback (*n* = 16)	**Suggestions**	6	10	6	“No. They were precise and punctual.”

	Item	*n*	Missing	No suggestions	Answers
Whole intervention (*n* = 28)	**Most useful aspect**	15	13	/	"Filling in the diary every time I took a medication helped me remember to take the medications themselves." "The reminders." (n = 4) "The diaries are very useful." "The diaries." "I believe that establishing an ongoing relationship gives us reassurance that we are being taken into account, not only as patients but also as people, and makes us feel listened to." "Staff feedback." "I have never had problems with adherence to therapy; however, for those who are concerned about taking it and about side effects, it is very useful to feel the closeness of an expert who reminds them to take it and recommends adherence." "The weekly schedule is an excellent interval. It keeps one constantly 'on track.' I believe it is very useful for many people, as it makes them feel observed and supported. Personally, I think it did not affect my adherence to therapy because I am already diligent and consistent, but I certainly participated with pleasure." "It keeps my attention on the therapy constantly." "When I was late submitting the diaries, I was called or reminded by the doctor (psychologist) who reminded me of the deadline." "To feel the closeness and involvement in my commitment to take care of myself." "The questionnaires were extremely useful, as they made me reflect on the true state of the disease, my own condition, and the symptom after therapy. It was helpful to think about my health status and to change strategies to live better with this illness and reduce anxieties. The meetings with the psychologist were extremely useful."

	Item	*n*	Missing	No suggestions	Answers
Critics/ negative aspects (*N* = 32)	**Problematic/ unhelpful aspects**	18	14	11	"Difficulties in completing the diaries." "The lack of in-person meetings. Useful for research to see how the patients reacts to their therapy. Personal meetings would be useful. The support from the psychologist was very helpful." "The paper forms have always been a limitation for me. I am often away for work, so I ended up noting everything on my phone and then transcribing it later." "The completion of the paper questionnaires [t.n., diaries]." "Manual completion." "Minimal difficulties with sending images of the paper diaries." "In the questionnaire responses, I noticed that there is never the option to indicate that some aspects have even improved in my perception of life as a cancer patient."

	Item	*n*	Missing	No suggestions	Answers
	Limitations	14	18	6	"Only computer-based questionnaires; talking with a doctor would be helpful." "Maybe going over the side effects again." "Feeling in the diaries means putting in writing one's emotional state; it is not always easy to face one's awareness and condition. The relationship with the therapy can be one of love and hate: on one hand it gives security, on the other we may want to stop taking it, but perhaps without it we would feel anxious about no longer being protected by its effect…" "The limitations of the project are that it is not focused on the patient, but only on the project itself, without giving the patient the opportunity to learn ways to improve their own condition. It would be useful to have personal sessions with the psychologist, which would also increase knowledge for research. I am available to participate in other psychological project. Thank you." "The paper format." "I think it is fairly easy for me to be consistent in taking my medication due to a strong motivation to be there for the people who love me, and also because the side effects are manageable for me. I believe that others who suffer more from the consequences of treatment can gain strength from feeling consistently supported." "What was reported in the previous point [t.n., no option to report improvements in condition in the questionnaires]." "If we are faced with a patient who does not take the therapy, filling in the diaries and the messages, I don't think, are sufficient, and this can be a limitation. Therefore, it would be better to meet in person every so often and ask how the therapy is progressing."

t.n. = translator's note

Appendix 12. *Study 5, distribution of satisfaction and perceived usefulness questionnaire scores.*

	Item	Max	*n*
Medication diaries (*N* = 32)	**Was keeping the diaries useful in supporting your adherence?**	1	1
		2	4
		3	3
		4	9
		5	8
		Missing	7
	How satisfied are you with the diaries?	1	1
		2	2
		3	5
		4	10
		5	7
		Missing	7
Educational material (*n* = 16)	**Did you read the material?**	0 (No)	2
		1 (Yes)	12
		Missing	2
	How clear was it?	1	1
		2	/
		3	/
		4	2
		5	10
		Missing	3
	Was it useful?	1	1
		2	/
		3	3
		4	4
		5	5
		Missing	3
	How satisfied are you with it?	1	1
		2	/
		3	1
		4	4
		5	7
		Missing	3
		1	/

	Item	Max	*n*
Personalised reminders (*n* = 16)	**Where the reminders useful in supporting your adherence?**	2	/
		3	3
		4	4
		5	6
		Missing	3
	How satisfied are you with them?	1	/
		2	/
		3	4
		4	3
		5	6
		Missing	3
Behavioural feedback (*n* = 16)	**Was the feedback useful in supporting your adherence?**	1	/
		2	/
		3	4
		4	4
		5	2
		Missing	6
	How satisfied are you with it?	1	/
		2	/
		3	1
		4	6
		5	3
		Missing	6
Whole intervention (*n* = 28)	**Did the intervention meet your needs?**	1	/
		2	1
		3	4
		4	10
		5	7
		Missing	6
	Do you think it could be beneficial for others in a similar condition?	1	/
		2	1
		3	2
		4	8
		5	11
		Missing	6
		1	/

	Item	Max	*n*
Study participation (*n* = 32)	**How easy was it for you to take part in the study?**	2	/
		3	3
		4	4
		5	18
		Missing	7
	Did you feel comfortable while participating?	1	/
		2	/
		3	3
		4	3
		5	19
		Missing	7
	Was the time commitment adequate?	1	/
		2	/
		3	5
		4	2
		5	18
		Missing	7

Abrahams, H. J. G., Knoop, H., Schreurs, M., Aaronson, N. K., Jacobsen, P. B., Newton, R. U., Courneya, K. S., Aitken, J. F., Arving, C., Brandberg, Y., Chambers, S. K., Gielissen, M. F. M., Glimelius, B., Goedendorp, M. M., Graves, K. D., Heiney, S. P., Horne, R., Hunter, M. S., Johansson, B., … Buffart, L. M. (2020). Moderators of the effect of psychosocial interventions on fatigue in women with breast cancer and men with prostate cancer: Individual patient data meta-analyses. *Psycho-Oncology*, *29*(11), 1772–1785. https://doi.org/10.1002/pon.5522

Ajzen, I. (1991). The theory of planned behavior. *Organizational Behavior and Human Decision Processes*, *50*(2), 179–211. https://doi.org/10.1016/0749-5978(91)90020-T

Akilandasowmya, G., Nirmaladevi, G., Suganthi, SU., & Aishwariya, A. (2024). Skin cancer diagnosis: Leveraging deep hidden features and ensemble classifiers for early detection and classification. *Biomedical Signal Processing and Control*, *88*, 105306. https://doi.org/10.1016/j.bspc.2023.105306

Al Kuwaiti, A., Nazer, K., Al-Reedy, A., Al-Shehri, S., Al-Muhanna, A., Subbarayalu, A. V., Al Muhanna, D., & Al-Muhanna, F. A. (2023). A Review of the Role of Artificial Intelligence in Healthcare. *Journal of Personalized Medicine*, *13*(6), 951. https://doi.org/10.3390/jpm13060951

Alba, A. C., Agoritsas, T., Walsh, M., Hanna, S., Iorio, A., Devereaux, P. J., McGinn, T., & Guyatt, G. (2017). Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *JAMA*, *318*(14), 1377–1384. https://doi.org/10.1001/jama.2017.12126

Anderson, L. J., Nuckols, T. K., Coles, C., Le, M. M., Schnipper, J. L., Shane, R., Jackevicius, C., Lee, J., Pevnick, J. M., & Members of the PHARM-DC Group. (2020). A systematic overview of systematic reviews evaluating medication adherence interventions. *American Journal of Health-System Pharmacy*, *77*(2), 138–147. https://doi.org/10.1093/ajhp/zxz284

Antoni, M. H. (2003). *Stress management intervention for women with breast cancer* (pp. xvi, 215). American Psychological Association. https://doi.org/10.1037/10488-000

Arch, J. J., Crespi, C. M., Levin, M. E., Genung, S. R., Nealis, M., Mitchell, J. L., Bright, E. E., Albright, K., Magidson, J. F., & Stanton, A. L. (2022). Randomized Controlled Pilot Trial of a Low-Touch Remotely-Delivered Values Intervention to Promote Adherence to Adjuvant Endocrine Therapy Among Breast Cancer Survivors. *Annals of Behavioral Medicine*, *56*(8), 856–871. https://doi.org/10.1093/abm/kaab118

Argentero, P., Torchio, E., Tibaldi, G., Horne, R., Clatworthy, J., & Munizza, C. (2010). [The beliefs about drug treatment. The Italian version of the BMQ (the Beliefs about Medicines Questionnaire): Its validity and applicability]. *Epidemiologia E Psichiatria Sociale*, *19*(1), 86–92.

Arigo, D., Jake-Schoffman, D. E., & Pagoto, S. L. (2024). The recent history and near future of digital health in the field of behavioral medicine: An update on progress from 2019 to 2024. *Journal of Behavioral Medicine*, *48*(1), 120–136. https://doi.org/10.1007/s10865-024-00526-x

Armitage, C. J., & Conner, M. (2000). Social cognition models and health behaviour: A structured review. *Psychology & Health*, *15*(2), 173–189. https://doi.org/10.1080/08870440008400299

Atkins, L., & Fallowfield, L. (2006). Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *European Journal of Cancer*, *42*(14), 2271–2276. https://doi.org/10.1016/j.ejca.2006.03.004

Bajwa, J., Munir, U., Nori, A., & Williams, B. (2021). Artificial intelligence in healthcare: Transforming the practice of medicine. *Future Healthcare Journal*, *8*(2), e188–e194. https://doi.org/10.7861/fhj.2021-0095

Balazard, F., Bertaut, A., Bordet, É., Mulard, S., Blanc, J., Briot, N., Paux, G., Dhaini Merimeche, A., Rigal, O., Coutant, C., Fournier, M., Jouannaud, C., Soulie, P., Lerebours, F., Cottu, P.-H., Tredan, O., Vanlemmens, L., Levy, C., Mouret-Reynier,

M.-A., … Pistilli, B. (2023). Adjuvant endocrine therapy uptake, toxicity, quality of life, and prediction of early discontinuation. *JNCI: Journal of the National Cancer Institute*, *115*(9), 1099–1108. https://doi.org/10.1093/jnci/djad109

Bandura, A. (1982). Self-efficacy mechanism in human agency. *American Psychologist*, *37*(2), 122–147. https://doi.org/10.1037/0003-066X.37.2.122

Bandura, A. (1998). Health promotion from the perspective of social cognitive theory. *Psychology & Health*, *13*(4), 623–649. https://doi.org/10.1080/08870449808407422

Barisone, M. G., Lerda, S., Ansaldi, S., Vincenzo, E. D., & Angelini, G. (2004). Psicopatologia ed epilessia: Esperienza clinica presso un Centro per la Diagnosi e la Cura dell'epilessia. *Official Journal of the Italian Society of Psychopathology*. https://old.jpsychopathol.it/article/psicopatologia-ed-epilessia-esperienza-clinica-presso-un-centro-per-la-diagnosi-e-la-cura-dellepilessia/

Basharat, I., & Shahid, S. (2024). AI-enabled chatbots healthcare systems: An ethical perspective on trust and reliability. *Journal of Health Organization and Management*, *ahead-of-print*(ahead-of-print). https://doi.org/10.1108/JHOM-10-2023-0302

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II.* (2ª ed.). Psychological Corporation. https://www.nctsn.org/measures/beck-depression-inventory-second-edition

Beckwée, D., Leysen, L., Meuwis, K., & Adriaenssens, N. (2017). Prevalence of aromatase inhibitor-induced arthralgia in breast cancer: A systematic review and meta-analysis. *Supportive Care in Cancer*, *25*(5), 1673–1686. https://doi.org/10.1007/s00520-017-3613-z

Bekbolatova, M., Mayer, J., Ong, C. W., & Toma, M. (2024). Transformative Potential of AI in Healthcare: Definitions, Applications, and Navigating the Ethical Landscape and Public Perspectives. *Healthcare*, *12*(2), Articolo 2. https://doi.org/10.3390/healthcare12020125

Bergua, V., Meillon, C., Potvin, O., Bouisson, J., Goff, M. L., Rouaud, O., Ritchie, K., Dartigues, J.-F., & Amieva, H. (2012). The STAI-Y trait scale: Psychometric properties and normative data from a large population-based study of elderly people. *International Psychogeriatrics*, *24*(7), 1163–1171. https://doi.org/10.1017/S1041610212000300

Bhandari, S., Ngo, P., Kute, B., Mandadi, M., Pitman, W. A., Wu, X., Lloyd, S., Brown, M. C., Rai, S. N., Jain, D., & Riley, E. C. (2019). Adherence to anti-estrogen therapy in women with hormone receptor-positive breast cancer utilizing bubble packaging: A pilot study. *Breast Cancer Research and Treatment*, *177*(2), 395–399. https://doi.org/10.1007/s10549-019-05308-7

Bhattacharya, S., Saleem, S. M., Singh, A., Singh, S., & Tripathi, S. (2024). Empowering precision medicine: Regenerative AI in breast cancer. *Frontiers in Oncology*, *14*, 1465720. https://doi.org/10.3389/fonc.2024.1465720

Bibault, J.-E., Chaix, B., Guillemassé, A., Cousin, S., Escande, A., Perrin, M., Pienkowski, A., Delamon, G., Nectoux, P., & Brouard, B. (2019). A Chatbot Versus Physicians to Provide Information for Patients With Breast Cancer: Blind, Randomized Controlled Noninferiority Trial. *Journal of Medical Internet Research*, *21*(11), e15787. https://doi.org/10.2196/15787

Bluethmann, S. M., Truica, C., Klepin, H. D., Olsen, N., Sciamanna, C., Chinchilli, V. M., & Schmitz, K. H. (2021). Study design and methods for the using exercise to relieve joint pain and improve AI adherence in older breast cancer survivors (REJOIN) trial. *Journal of Geriatric Oncology*, *12*(7), 1146–1153. https://doi.org/10.1016/j.jgo.2021.05.011

Boughner, R. L. (2010). Volunteer Bias. In *Encyclopedia of Research Design* (pp. 1609–1610). SAGE Publications, Inc. https://doi.org/10.4135/9781412961288

Bridle, C., Riemsma ,R. P., Pattenden ,J., Sowden ,A. J., Mather ,L., Watt ,I. S., & and Walker, A. (2005). Systematic review of the effectiveness of health behavior

interventions based on the transtheoretical model. *Psychology & Health*, *20*(3), 283–301. https://doi.org/10.1080/08870440512331333997

Brown, M. T., & Bussell, J. K. (2011). Medication Adherence: WHO Cares? *Mayo Clinic Proceedings*, *86*(4), 304–314. https://doi.org/10.4065/mcp.2010.0575

Cahir, C., Barron, T. I., Sharp, L., & Bennett, K. (2017). Can demographic, clinical and treatment-related factors available at hormonal therapy initiation predict non-persistence in women with stage I–III breast cancer? *Cancer Causes & Control*, *28*(3), 215–225. https://doi.org/10.1007/s10552-017-0851-9

Cai, J., Divino, V., & Burudpakdee, C. (2017). Adherence and persistence in patients with type 2 diabetes mellitus newly initiating canagliflozin, dapagliflozin, dpp-4s, or glp-1s in the United States. *Current Medical Research and Opinion*. https://www.tandfonline.com/doi/abs/10.1080/03007995.2017.1320277

Cankurtaran, E. s., Ozalp, E., Soygur, H., Ozer, S., Akbiyik, D. i., & Bottomley, A. (2008). Understanding the reliability and validity of the EORTC QLQ-C30 in Turkish cancer patients. *European Journal of Cancer Care*, *17*(1), 98–104. https://doi.org/10.1111/j.1365-2354.2007.00827.x

Carter, J. V., Pan, J., Rai, S. N., & Galandiuk, S. (2016). ROC-ing along: Evaluation and interpretation of receiver operating characteristic curves. *Surgery*, *159*(6), 1638–1645. https://doi.org/10.1016/j.surg.2015.12.029

Chaix, B., Bibault, J.-E., Pienkowski, A., Delamon, G., Guillemassé, A., Nectoux, P., & Brouard, B. (2019). When Chatbots Meet Patients: One-Year Prospective Study of Conversations Between Patients With Breast Cancer and a Chatbot. *JMIR Cancer*, *5*(1), e12856. https://doi.org/10.2196/12856

Chakraborty, D., Bailey, B. A., Seidler, A. L., Yoong, S., Hunter, K. E., Hodder, R. K., Webster, A. C., & Johnson, B. J. (2022). Exploring the application of behaviour change technique taxonomies in childhood obesity prevention interventions: A systematic scoping review. *Preventive Medicine Reports*, *29*, 101928. https://doi.org/10.1016/j.pmedr.2022.101928

Chalela, P., Munoz, E., Inupakutika, D., Kaghyan, S., Akopian, D., Kaklamani, V., Lathrop, K., & Ramirez, A. (2018). Improving adherence to endocrine hormonal therapy among breast cancer patients: Study protocol for a randomized controlled trial. *Contemporary Clinical Trials Communications*, *12*, 109–115. https://doi.org/10.1016/j.conctc.2018.10.001

Chantzaras, A., & Yfantopoulos, J. (2025). Determinants of medication adherence in patients with diabetes, hypertension, and hyperlipidemia. *Hormones*. https://doi.org/10.1007/s42000-025-00631-9

Chaput, G., & Sumar, N. (2022). Endocrine therapies for breast and prostate cancers. *Canadian Family Physician*, *68*(4), 271–276. https://doi.org/10.46747/cfp.6804271

Chen, J. H., & Asch, S. M. (2017). Machine Learning and Prediction in Medicine—Beyond the Peak of Inflated Expectations. *New England Journal of Medicine*, *376*(26), 2507–2509. https://doi.org/10.1056/NEJMp1702071

Chew, H. S. J., Chew, N. W., Loong, S. S. E., Lim, S. L., Tam, W. S. W., Chin, Y. H., Chao, A. M., Dimitriadis, G. K., Gao, Y., So, J. B. Y., Shabbir, A., & Ngiam, K. Y. (2024). Effectiveness of an Artificial Intelligence-Assisted App for Improving Eating Behaviors: Mixed Methods Evaluation. *Journal of Medical Internet Research*, *26*(1), e46036. https://doi.org/10.2196/46036

Chin, M. H., Afsar-Manesh, N., Bierman, A. S., Chang, C., Colón-Rodríguez, C. J., Dullabh, P., Duran, D. G., Fair, M., Hernandez-Boussard, T., Hightower, M., Jain, A., Jordan, W. B., Konya, S., Moore, R. H., Moore, T. T., Rodriguez, R., Shaheen, G., Snyder, L. P., Srinivasan, M., … Ohno-Machado, L. (2023). Guiding Principles to Address the Impact of Algorithm Bias on Racial and Ethnic Disparities in Health and Health Care. *JAMA Network Open*, *6*(12), e2345050. https://doi.org/10.1001/jamanetworkopen.2023.45050

Collins, G. S., Dhiman, P., Ma, J., Schlussel, M. M., Archer, L., Calster, B. V., Harrell, F. E., Martin, G. P., Moons, K. G. M., Smeden, M. van, Sperrin, M., Bullock, G. S., &

Riley, R. D. (2024). *Evaluation of clinical prediction models (part 1): From development to external validation*. https://doi.org/10.1136/bmj-2023-074819

Collins, L. M., Dziak, J. J., & Li, R. (2009). Design of experiments with multiple independent variables: A resource management perspective on complete and reduced factorial designs. *Psychological Methods*, *14*(3), 202–224. https://doi.org/10.1037/a0015826

Communication from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions on Artificial Intelligence for Europe (2018). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2018%3A237%3AFIN#document1

Conley, C. C., McIntyre, M., Pensak, N. A., Lynce, F., Graham, D., Ismail-Khan, R., Lopez, K., Vadaparampil, S. T., & O'Neill, S. C. (2022). Barriers and facilitators to taking CDK4/6 inhibitors among patients with metastatic breast cancer: A qualitative study. *Breast Cancer Research and Treatment*, *192*(2), 385–399. https://doi.org/10.1007/s10549-022-06518-2

Conn, V. S., & Ruppar, T. M. (2017). Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. *Preventive Medicine*, *99*, 269–276. https://doi.org/10.1016/j.ypmed.2017.03.008

Conner, M., & Norman, P. (1998). Editorial: Social cognition models in health psychology. *Psychology & Health*, *13*(2), 179–185. https://doi.org/10.1080/08870449808406745

Corter, A. L., Findlay, M., Broom, R., Porter, D., & Petrie, K. J. (2013). Beliefs about medicine and illness are associated with fear of cancer recurrence in women taking adjuvant endocrine therapy for breast cancer. *British Journal of Health Psychology*, *18*(1), 168–181. https://doi.org/10.1111/bjhp.12003

Cramer, J. A., Roy, A., Burrell, A., Fairchild, C. J., Fuldeore, M. J., Ollendorf, D. A., & Wong, P. K. (2008). Medication compliance and persistence: Terminology and

definitions. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *11*(1), 44–47. https://doi.org/10.1111/j.1524-4733.2007.00213.x

Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., & Garcia-Cardenas, V. (2018). Economic impact of medication non-adherence by disease groups: A systematic review. *BMJ Open*, *8*(1), e016982. https://doi.org/10.1136/bmjopen-2017-016982

Delea, T. E., Kartashov, A., & Sharma, P. P. (2014). Retrospective Study of the Prevalence, Predictors, and Consequences of Nonadherence With Lapatinib in Women With Metastatic Breast Cancer Who Were Previously Treated With Trastuzumab. *The Journal of Pharmacy Technology: jPT: Official Publication of the Association of Pharmacy Technicians*, *30*(1), 21–30. https://doi.org/10.1177/8755122513513428

Donovan, G., Hall, N., Ling, J., Smith, F., & Wilkes, S. (2022). Influencing medication taking behaviors using automated two-way digital communication: A narrative synthesis systematic review informed by the Behavior Change Wheel. *British Journal of Health Psychology*, *27*(3), 861–890. https://doi.org/10.1111/bjhp.12580

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology & Community Health*, *52*(6), 377–384. https://doi.org/10.1136/jech.52.6.377

Drewes, C., Kirkovits, T., Schiltz, D., Schinkoethe, T., Haidinger, R., Goldmann-Posch, U., Harbeck, N., & Wuerstlein, R. (2016). EHealth Acceptance and New Media Preferences for Therapy Assistance Among Breast Cancer Patients. *JMIR Cancer*, *2*(2), e5711. https://doi.org/10.2196/cancer.5711

Duff, O. M., Walsh, D. M., Furlong, B. A., O'Connor, N. E., Moran, K. A., & Woods, C. B. (2017). Behavior Change Techniques in Physical Activity eHealth Interventions for People With Cardiovascular Disease: Systematic Review. *Journal of Medical Internet Research*, *19*(8), e7782. https://doi.org/10.2196/jmir.7782

Ell, K., Vourlekis, B., Xie, B., Nedjat-Haiem, F. R., Lee, P.-J., Muderspach, L., Russell, C., & Palinkas, L. A. (2009). Cancer treatment adherence among low-income women with breast or gynecologic cancer. *Cancer*, *115*(19), 4606–4615. https://doi.org/10.1002/cncr.24500

Elting, L. S., & Shih, Y.-C. T. (2004). The economic burden of supportive care of cancer patients. *Supportive Care in Cancer*, *12*(4), 219–226. https://doi.org/10.1007/s00520-003-0513-1

Engel, T., Ungar, B., Ben-Haim, G., Levhar, N., Eliakim, R., & Ben-Horin, S. (2017). Re-phrasing the question: A simple tool for evaluation of adherence to therapy in patients with inflammatory bowel disease. *United European Gastroenterology Journal*, *5*(6), 880–886. https://doi.org/10.1177/2050640616687838

Fang, Y., Jiang, Z., Han, Z., & Xiang, X. (2025). Barriers and facilitators to medication adherence in patients after PCI surgery: A mixed-methods systematic review. *Heart & Lung*, *72*, 57–64. https://doi.org/10.1016/j.hrtlng.2025.03.008

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. *International Journal of Cancer*. https://doi.org/10.1002/ijc.33588

Ferraris, C., Ballestra, B., Listorti, C., Cappelletti, V., Reduzzi, C., Scaperrotta, G. P., Pulice, I., Ferrari, E. G. A., Folli, S., Mariani, L., & Martelli, G. (2020). Red clover and lifestyle changes to contrast menopausal symptoms in premenopausal patients with hormone-sensitive breast cancer receiving tamoxifen. *Breast Cancer Research and Treatment*, *180*(1), 157–165. https://doi.org/10.1007/s10549-020-05534-4

Finitsis, D. J., Vose, B. A., Mahalak, J. G., & Salner, A. L. (2019). Interventions to promote adherence to endocrine therapy among breast cancer survivors: A meta-analysis. *Psycho-Oncology*, *28*(2), 255–263. https://doi.org/10.1002/pon.4959

Foot, H., La Caze, A., Gujral, G., & Cottrell, N. (2016). The necessity–concerns framework predicts adherence to medication in multiple illness conditions: A meta-

analysis. *Patient Education and Counseling*, *99*(5), 706–717. https://doi.org/10.1016/j.pec.2015.11.004

Fragomeni, S. M., Sciallis, A., & Jeruss, J. S. (2018). Molecular subtypes and local-regional control of breast cancer. *Surgical oncology clinics of North America*, *27*(1), 95–120. https://doi.org/10.1016/j.soc.2017.08.005

Gast, A., & Mathes, T. (2019). Medication adherence influencing factors—An (updated) overview of systematic reviews. *Systematic Reviews*, *8*(1), 112. https://doi.org/10.1186/s13643-019-1014-8

Gawankar, S., Nair, S., Pawar, V., Vhatkar, A., & Chavan, P. (2024). Patient Privacy and Data Security in the Era of AI-Driven Healthcare. *2024 8th International Conference on Computing, Communication, Control and Automation (ICCUBEA)*, 1–6. https://doi.org/10.1109/ICCUBEA61740.2024.10775004

Getachew, S., Addissie, A., Seife, E., Wakuma, T., Unverzagt, S., Jemal, A., Taylor, L., Wienke, A., & Kantelhardt, E. J. (2022). Breast Nurse Intervention to Improve Adherence to Endocrine Therapy Among Breast Cancer Patients in South Ethiopia. *The Oncologist*, *27*(8), e650–e660. https://doi.org/10.1093/oncolo/oyac081

Given, B. A., Spoelstra, S. L., & Grant, M. (2011). The Challenges of Oral Agents as Antineoplastic Treatments. *Seminars in Oncology Nursing*, *27*(2), 93–103. https://doi.org/10.1016/j.soncn.2011.02.003

Graetz, I., McKillop, C. N., Stepanski, E., Vidal, G. A., Anderson, J. N., & Schwartzberg, L. S. (2018). Use of a web-based app to improve breast cancer symptom management and adherence for aromatase inhibitors: A randomized controlled feasibility trial. *Journal of Cancer Survivorship*, *12*(4), 431–440. https://doi.org/10.1007/s11764-018-0682-z

Greer, J. A., Amoyal, N., Nisotel, L., Fishbein, J. N., MacDonald, J., Stagl, J., Lennes, I., Temel, J. S., Safren, S. A., & Pirl, W. F. (2016). A Systematic Review of Adherence to Oral Antineoplastic Therapies. *The Oncologist*, *21*(3), 354–376. https://doi.org/10.1634/theoncologist.2015-0405

Grunfeld, E. A., Hunter, M. S., Sikka, P., & Mittal, S. (2005). Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Education and Counseling*, *59*(1), 97–102. https://doi.org/10.1016/j.pec.2004.10.005

Gu, X., Shen, X., Zhou, J.-R., Chu, J.-H., & Jiang, L. (2024). The effects of common-sense model interventions on cancer patients: A systematic review. *Medicine*, *103*(17), e37777. https://doi.org/10.1097/MD.0000000000037777

Guangyu, Z., & Xinghua, L. (2024). Health Psychology. In *The ECPH Encyclopedia of Psychology* (pp. 608–609). Springer, Singapore. https://doi.org/10.1007/978-981-97-7874-4_769

Guastaferro, K., & Collins, L. M. (2021). Optimization Methods and Implementation Science: An Opportunity for Behavioral and Biobehavioral Interventions. *Implementation Research and Practice*, *2*, 26334895211054363. https://doi.org/10.1177/26334895211054363

Hadji, P., Blettner, M., Harbeck, N., Jackisch, C., Lück, H.-J., Windemuth-Kieselbach, C., Zaun, S., & Kreienberg, R. (2013). The Patient's Anastrozole Compliance to Therapy (PACT) Program: A randomized, in-practice study on the impact of a standardized information program on persistence and compliance to adjuvant endocrine therapy in postmenopausal women with early breast cancer†. *Annals of Oncology*, *24*(6), 1505–1512. https://doi.org/10.1093/annonc/mds653

Hagger, M. S. (2025). Psychological Determinants of Health Behavior. *Annual Review of Psychology*, *76*(Volume 76, 2025), 821–850. https://doi.org/10.1146/annurev-psych-020124-114222

Hagger, M. S., & Orbell, S. (2022). The common sense model of illness self-regulation: A conceptual review and proposed extended model. *Health Psychology Review*, *16*(3), 347–377. https://doi.org/10.1080/17437199.2021.1878050

Hayes, S. C., Luoma, J. B., Bond, F. W., Masuda, A., & Lillis, J. (2006). Acceptance and Commitment Therapy: Model, processes and outcomes. *Behaviour Research and Therapy*, *44*(1), 1–25. https://doi.org/10.1016/j.brat.2005.06.006

Heiney, S. P., Parker, P. D., Felder, T. M., Adams, S. A., Omofuma, O. O., & Hulett, J. M. (2019). A systematic review of interventions to improve adherence to endocrine therapy. *Breast Cancer Research and Treatment*, *173*(3), 499–510. https://doi.org/10.1007/s10549-018-5012-7

Heisig, S. R., Shedden-Mora, M. C., von Blanckenburg, P., Schuricht, F., Rief, W., Albert, U.-S., & Nestoriuc, Y. (2015). Informing women with breast cancer about endocrine therapy: Effects on knowledge and adherence. *Psycho-Oncology*, *24*(2), 130–137. https://doi.org/10.1002/pon.3611

Henry, N. L., Azzouz, F., Desta, Z., Li, L., Nguyen, A. T., Lemler, S., Hayden, J., Tarpinian, K., Yakim, E., Flockhart, D. A., Stearns, V., Hayes, D. F., & Storniolo, A. M. (2012). Predictors of Aromatase Inhibitor Discontinuation as a Result of Treatment-Emergent Symptoms in Early-Stage Breast Cancer. *Journal of Clinical Oncology*, *30*(9), 936–942. https://doi.org/10.1200/JCO.2011.38.0261

Hershman, D. L., Unger, J. M., Hillyer, G. C., Moseley, A., Arnold, K. B., Dakhil, S. R., Esparaz, B. T., Kuan, M. C., Graham, M. L., Lackowski, D. M., Edenfield, W. J., Dayao, Z. R., Henry, N. L., Gralow, J. R., Ramsey, S. D., & Neugut, A. I. (2020). Randomized Trial of Text Messaging to Reduce Early Discontinuation of Adjuvant Aromatase Inhibitor Therapy in Women With Early-Stage Breast Cancer: SWOG S1105. *Journal of Clinical Oncology*, *38*(19), 2122–2129. https://doi.org/10.1200/JCO.19.02699

Holmes, E. A. F., Hughes, D. A., & Morrison, V. L. (2014). Predicting Adherence to Medications Using Health Psychology Theories: A Systematic Review of 20 Years of Empirical Research. *Value in Health*, *17*(8), 863–876. https://doi.org/10.1016/j.jval.2014.08.2671

Hooper J., Wilcox H., & Wheeler E. (2024). *Reducing inequalities in metastatic breast cancer care: An overview.*

Hooper, P., Jutai, J. W., Strong, G., & Russell-Minda, E. (2008). Age-related macular degeneration and low-vision rehabilitation: A systematic review. *Canadian Journal of Ophthalmology*, *43*(2), 180–187. https://doi.org/10.3129/i08-001

Horne, R., Chapman, S. C. E., Parham, R., Freemantle, N., Forbes, A., & Cooper, V. (2013). Understanding Patients' Adherence-Related Beliefs about Medicines Prescribed for Long-Term Conditions: A Meta-Analytic Review of the Necessity-Concerns Framework. *PLOS ONE*, *8*(12), e80633. https://doi.org/10.1371/journal.pone.0080633

Horne, R., & Weinman, J. (1998). Predicting Treatment Adherence: An Overview of Theoretical Models. In *Adherence to Treatment in Medical Conditions* (1ª ed.). CRC Press. https://www.taylorfrancis.com/chapters/edit/10.1201/9781003072348-4/predicting-treatment-adherence-overview-theoretical-models-robert-horne-john-weinman

Horne, R., & Weinman, J. (1999). Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *Journal of Psychosomatic Research*, *47*(6), 555–567. https://doi.org/10.1016/S0022-3999(99)00057-4

Horne, R., & Weinman, J. (2002). Self-regulation and Self-management in Asthma: Exploring The Role of Illness Perceptions and Treatment Beliefs in Explaining Non-adherence to Preventer Medication. *Psychology & Health*, *17*(1), 17–32. https://doi.org/10.1080/08870440290001502

Horne, R., Weinman ,John, & and Hankins, M. (1999). The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology & Health*, *14*(1), 1–24. https://doi.org/10.1080/08870449908407311

Humphreys, G., Evans, R., Makin, H., Cooke, R., & Jones, A. (2021). Identification of Behavior Change Techniques From Successful Web-Based Interventions Targeting Alcohol Consumption, Binge Eating, and Gambling: Systematic Review. *Journal of Medical Internet Research*, *23*(2), e22694. https://doi.org/10.2196/22694

Hurtado-de-Mendoza, A., Cabling, M. L., Lobo, T., Dash, C., & Sheppard, V. B. (2016). Behavioral Interventions to Enhance Adherence to Hormone Therapy in Breast Cancer Survivors: A Systematic Literature Review. *Clinical Breast Cancer*, *16*(4), 247-255.e3. https://doi.org/10.1016/j.clbc.2016.03.006

Husinka, L., Koerner ,Pamela H., Miller ,Rick T., & and Trombatt, W. (2021). Review of cyclin-dependent kinase 4/6 inhibitors in the treatment of advanced or metastatic breast cancer. *Journal of Drug Assessment*, *10*(1), 27–34. https://doi.org/10.1080/21556660.2020.1857103

Hwang, K.-S., Lee, K.-H., Yang, C.-M., Lee, H.-J., & Lee, S.-Y. (2023). *Effects of Psychosocial Interventions for Patients with Breast Cancer: A Meta-analysis*. *21*(1), 118–125. https://doi.org/10.9758/cpn.2023.21.1.118

Ilardi, C. R., Gamboz, N., Iavarone, A., Chieffi, S., & Brandimonte, M. A. (2021). Psychometric properties of the STAI-Y scales and normative data in an Italian elderly population. *Aging Clinical and Experimental Research*, *33*(10), 2759–2766. https://doi.org/10.1007/s40520-021-01815-0

Imeri, H., Toth, J., Arnold, A., & Barnard, M. (2022). Use of the transtheoretical model in medication adherence: A systematic review. *Research in Social and Administrative Pharmacy*, *18*(5), 2778–2785. https://doi.org/10.1016/j.sapharm.2021.07.008

Inotai, A., Ágh, T., Maris, R., Erdősi, D., Kovács, S., Kaló, Z., & Senkus, E. (2021). Systematic review of real-world studies evaluating the impact of medication non-adherence to endocrine therapies on hard clinical endpoints in patients with non-metastatic breast cancer. *Cancer Treatment Reviews*, *100*, 102264. https://doi.org/10.1016/j.ctrv.2021.102264

Jackson, C., Eliasson, Â. L., Barber, N., & Weinman, J. (2014). Applying COM-B to medication adherence: A suggested framework for research and interventions. *European Health Psychologist*, *16*(1), Articolo 1.

Jackson, C., Eliasson, L., & Weinman, J. (2014). *Applying COM-B to medication adherence*. https://www.semanticscholar.org/paper/Applying-COM-B-to-

medication-adherence-Jackson-Eliasson/bfdb62f5430b90243959e8a989abf5ddb12ee32b

Jacob, L., Hadji, P., Albert, U.-S., Kalder, M., & Kostev, K. (2015). Impact of disease management programs on women with breast cancer in Germany. *Breast Cancer Research and Treatment*, *153*(2), 391–395. https://doi.org/10.1007/s10549-015-3530-0

Jacobs, J. M., Post, K., Massad, K., Horick, N. K., Walsh, E. A., Cohn, J., Rapoport, C. S., Clara, A. J., Antoni, M. H., Safren, S. A., Partridge, A. H., Peppercorn, J. M., Park, E. R., Temel, J. S., & Greer, J. A. (2022). A telehealth intervention for symptom management, distress, and adherence to adjuvant endocrine therapy: A randomized controlled trial. *Cancer*, *128*(19), 3541–3551. https://doi.org/10.1002/cncr.34409

Johannsen, M., Farver, I., Beck, N., & Zachariae, R. (2013). The efficacy of psychosocial intervention for pain in breast cancer patients and survivors: A systematic review and meta-analysis. *Breast Cancer Research and Treatment*, *138*(3), 675–690. https://doi.org/10.1007/s10549-013-2503-4

Johnston, M., & Dixon, D. (2008). Current issues and new directions in psychology and health: What happened to behaviour in the decade of behaviour? *Psychology & Health*, *23*(5), 509–513. https://doi.org/10.1080/08870440701816728

Johnston, M., Weinman, J., & Chater, A. (2011). *A healthy contribution*. BPS. https://www.bps.org.uk/psychologist/healthy-contribution

Jones, C. J., Smith, H. E., & Llewellyn, C. D. (2016). A systematic review of the effectiveness of interventions using the Common Sense Self-Regulatory Model to improve adherence behaviours. *Journal of Health Psychology*, *21*(11), 2709–2724. https://doi.org/10.1177/1359105315583372

Jones, C. J., Smith ,Helen, & and Llewellyn, C. (2014). Evaluating the effectiveness of health belief model interventions in improving adherence: A systematic review. *Health Psychology Review*, *8*(3), 253–269. https://doi.org/10.1080/17437199.2013.802623

Jordan, J. L., Ellis, S. J., & Chambers, R. (2002). Defining shared decision making and concordance: Are they one and the same? *Postgraduate Medical Journal*, *78*(921), 383–384. https://doi.org/10.1136/pmj.78.921.383

Kabat-Zinn, J., Lipworth, L., & Burney, R. (1985). The clinical use of mindfulness meditation for the self-regulation of chronic pain. *Journal of Behavioral Medicine*, *8*(2), 163–190. https://doi.org/10.1007/BF00845519

Kaplan, R. M. (2009). Health Psychology: Where Are We And Where Do We Go From Here? *Mens Sana Monographs*, *7*(1), 3–9. https://doi.org/10.4103/0973-1229.43584

Karabulut, B., & Uslu, E. (2024). Schizophrenia and medication adherence: Associated factors. *Archives of Psychiatric Nursing*, *49*, 47–54. https://doi.org/10.1016/j.apnu.2024.01.015

Kaur, N., Gonzales, M., Alcaraz, C. G., Barnes, L. E., Wells, K. J., & Gong, J. (2021). Theory-Guided Randomized Neural Networks for Decoding Medication-Taking Behavior. *2021 IEEE EMBS International Conference on Biomedical and Health Informatics (BHI)*, 1–4. https://doi.org/10.1109/BHI50953.2021.9508614

Keyloun, K. R., Hansen, R. N., Hepp, Z., Gillard, P., Thase, M. E., & Devine, E. B. (2017). Adherence and Persistence Across Antidepressant Therapeutic Classes: A Retrospective Claims Analysis Among Insured US Patients with Major Depressive Disorder (MDD). *CNS Drugs*, *31*(5), 421–432. https://doi.org/10.1007/s40263-017-0417-0

Khan, N., Nauman, M., Almadhor, A. S., Akhtar, N., Alghuried, A., & Alhudhaif, A. (2024). Guaranteeing Correctness in Black-Box Machine Learning: A Fusion of Explainable AI and Formal Methods for Healthcare Decision-Making. *IEEE Access*, *12*, 90299–90316. https://doi.org/10.1109/ACCESS.2024.3420415

Kini, V., & Ho, P. M. (2018). Interventions to Improve Medication Adherence: A Review. *JAMA*, *320*(23), 2461–2473. https://doi.org/10.1001/jama.2018.19271

Komatsu, H., Yagasaki, K., Yamaguchi, T., Mori, A., Kawano, H., Minamoto, N., Honma, O., & Tamura, K. (2020). Effects of a nurse-led medication self-management

programme in women with oral treatments for metastatic breast cancer: A mixed-method randomised controlled trial. *European Journal of Oncology Nursing: The Official Journal of European Oncology Nursing Society*, *47*, 101780. https://doi.org/10.1016/j.ejon.2020.101780

Kondylakis, H., Koumakis, L., Tsiknakis, M., Marias, K., Genitsaridi, E., Pravettoni, G., Gorini, A., & Mazzocco, K. (2013). Smart Recommendation Services in Support of Patient Empowerment and Personalized Medicine. In G. A. Tsihrintzis, M. Virvou, & L. C. Jain (A c. Di), *Multimedia Services in Intelligent Environments: Recommendation Services* (pp. 39–61). Springer International Publishing. https://doi.org/10.1007/978-3-319-00375-7_4

Krok-Schoen, J. L., Naughton, M. J., Young, G. S., Moon, J., Poi, M., Melin, S. A., Wood, M. E., Hopkins, J. O., Paskett, E. D., & Post, D. M. (2019). Increasing Adherence to Adjuvant Hormone Therapy Among Patients With Breast Cancer: A Smart Phone App-Based Pilot Study. *Cancer Control*, *26*(1), 1073274819883287. https://doi.org/10.1177/1073274819883287

Krueger, R. A. (2014). *Focus Groups: A Practical Guide for Applied Research*. SAGE Publications.

Kuo, C., Wang, H., & Tseng, L. (2022). Using data mining technology to predict medication-taking behaviour in women with breast cancer: A retrospective study. *Nursing Open*, *9*(6), 2646–2656. https://doi.org/10.1002/nop2.963

Lai, J., Song, H., Ren, Y., Li, S., & Xiao, F. (2021). Effectiveness of Supportive-Expressive Group Therapy in Women with Breast Cancer: A Systematic Review and Meta-Analysis. *Oncology Research and Treatment*, *44*(5), 252–260. https://doi.org/10.1159/000515756

Lee, C., Check, D. K., Manace Brenman, L., Kushi, L. H., Epstein, M. M., Neslund-Dudas, C., Pawloski, P. A., Achacoso, N., Laurent, C., Fehrenbacher, L., & Habel, L. A. (2020). Adjuvant endocrine therapy for breast cancer patients: Impact of a health

system outreach program to improve adherence. *Breast Cancer Research and Treatment*, *180*(1), 219–226. https://doi.org/10.1007/s10549-020-05539-z

Lehane, E., & McCarthy, G. (2007). Intentional and unintentional medication non-adherence: A comprehensive framework for clinical research and practice? A discussion paper. *International Journal of Nursing Studies*, *44*(8), 1468–1477. https://doi.org/10.1016/j.ijnurstu.2006.07.010

LeVee, A., Deutsh, A., Lindgren, E. S., Yan, R., Moore, H., Pasricha, N. D., Leventhal, J., Dent, S., & Rugo, H. S. (2025). New Drugs, New Toxicities: Side Effects of New and Emerging Breast Cancer Therapies. *American Society of Clinical Oncology Educational Book*, *45*(3), e473384. https://doi.org/10.1200/EDBK-25-473384

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. https://doi.org/10.1007/s10865-016-9782-2

Leventhal, H., Weinman, J., Leventhal, E. A., & Phillips, L. A. (2008). Health Psychology: The Search for Pathways between Behavior and Health. *Annual Review of Psychology*, *59*(Volume 59, 2008), 477–505. https://doi.org/10.1146/annurev.psych.59.103006.093643

Lindroth, H., Nalaie, K., Raghu, R., Ayala, I. N., Busch, C., Bhattacharyya, A., Moreno Franco, P., Diedrich, D. A., Pickering, B. W., & Herasevich, V. (2024). Applied Artificial Intelligence in Healthcare: A Review of Computer Vision Technology Application in Hospital Settings. *Journal of Imaging*, *10*(4), Articolo 4. https://doi.org/10.3390/jimaging10040081

Magadza, C., Radloff, S. E., & Srinivas, S. C. (2009). The effect of an educational intervention on patients' knowledge about hypertension, beliefs about medicines, and adherence. *Research in Social and Administrative Pharmacy*, *5*(4), 363–375. https://doi.org/10.1016/j.sapharm.2009.01.004

Mamguem Kamga, A., Di Martino, C., Anota, A., Paget-Bailly, S., Coutant, C., Arveux, P., Desmoulins, I., & Dabakuyo-Yonli, T. S. (2020). Impact of routine assessment of health-related quality of life coupled with therapeutic information on compliance with endocrine therapy in patients with non-metastatic breast cancer: Protocol for a randomized controlled trial. *Trials*, *21*(1), 527. https://doi.org/10.1186/s13063-020-04397-w

Mann, E., Smith, M. J., Hellier, J., Balabanovic, J. A., Hamed, H., Grunfeld, E. A., & Hunter, M. S. (2012). Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): A randomised controlled trial. *The Lancet Oncology*, *13*(3), 309–318. https://doi.org/10.1016/S1470-2045(11)70364-3

Marcondes, L., Silva, L. dos S., de Oliveira Ribeiro, C., Oshiro, N. N., Nogueira, L. de A., Guimaraes, P. R. B., & Kalinke, L. P. (2024). Anxiety Levels in Brazilian Women with Metastatic Breast Cancer Undergoing Palliative Chemotherapy: A Prospective Study. *Asian Pacific Journal of Cancer Prevention : APJCP*, *25*(4), 1135–1141. https://doi.org/10.31557/APJCP.2024.25.4.1135

Markopoulos, C., Neven, P., Tanner, M., Marty, M., Kreienberg, R., Atkins, L., Franquet, A., Gnant, M., Neciosup, S., Tesarova, P., Barni, S., & Deschamp, V. (2015). Does patient education work in breast cancer? Final results from the global CARIATIDE study. *Future Oncology*, *11*(2), 205–217. https://doi.org/10.2217/fon.14.179

Marques, M. M., Wright, A. J., Corker, E., Johnston, M., West, R., Hastings, J., Zhang, L., & Michie, S. (2023). The Behaviour Change Technique Ontology: Transforming the Behaviour Change Technique Taxonomy v1. *Wellcome Open Research*, *8*, 308. https://doi.org/10.12688/wellcomeopenres.19363.1

Masiero, M., Spada, G. E., Fragale, E., Pezzolato, M., Munzone, E., Sanchini, V., Pietrobon, R., Teixeira, L., Valencia, M., Machiavelli, A., Woloski, R., Marzorati, C., & Pravettoni, G. (2024). Adherence to oral anticancer treatments: Network and sentiment analysis exploring perceived internal and external determinants in

patients with metastatic breast cancer. *Supportive Care in Cancer*, *32*(7), 458. https://doi.org/10.1007/s00520-024-08639-4

Masiero, M., Spada, G. E., Sanchini, V., Munzone, E., Pietrobon, R., Teixeira, L., Valencia, M., Machiavelli, A., Fragale, E., Pezzolato, M., & Pravettoni, G. (2023). A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial. *JMIR Research Protocols*, *12*(1), e48852. https://doi.org/10.2196/48852

Matakanye, H., & Grace Tshitangano, T. (2024). Enhancing TB treatment adherence through the application of the Behaviour Change Wheel. *Cogent Public Health*, *11*(1), 2376942. https://doi.org/10.1080/27707571.2024.2376942

May, R., & Denecke, K. (2022). Security, privacy, and healthcare-related conversational agents: A scoping review. *Informatics for Health and Social Care*, *47*(2), 194–210. https://doi.org/10.1080/17538157.2021.1983578

Mazzocco, K., Busacchio, D., Summers, P. E., Marzorati, C., Pricolo, P., Petralia, G., & Pravettoni, G. (2023). Is whole-body magnetic resonance imaging a source of anxiety in oncological patients? *Cancer Reports*, *6*(3), e1737. https://doi.org/10.1002/cnr2.1737

McGrady, M. E., Schwartz, L. E., Noser, A. E., Klages, K. L., Sweenie, R., Breen, G., & Ramsey, R. R. (2023). Systematic Evaluation of the Behavior Change Techniques and Quality of Commercially Available Cancer Self-Management Apps. *JCO Oncology Practice*, *19*(2), e228–e237. https://doi.org/10.1200/OP.22.00491

Meguerditchian, A., Tamblyn, R., Meterissian, S., Law, S., Prchal, J., Winslade, N., & Stern, D. (2016). Adjuvant Endocrine Therapy in Breast Cancer: A Novel e-Health Approach in Optimizing Treatment for Seniors (OPTIMUM): A Two-Group Controlled Comparison Pilot Study. *JMIR Research Protocols*, *5*(4), e6519. https://doi.org/10.2196/resprot.6519

Melilli, E., Díaz, M. I., Gomis-Pastor, M., González, E., Gutierrez-Dalmau, A., Nuño, E. I., Pérez, A. M., Plasencia, I., Sangrador, A., Lázaro, E., Montero, N., & Soria, C. (2025). Predictors of Treatment Adherence in Kidney Transplant Patients: A Systematic Review of the Literature. *Journal of Clinical Medicine*, *14*(5), 1622. https://doi.org/10.3390/jcm14051622

Meneveau, M. O., Keim-Malpass, J., Camacho, T. F., Anderson, R. T., & Showalter, S. L. (2020). Predicting adjuvant endocrine therapy initiation and adherence among older women with early-stage breast cancer. *Breast Cancer Research and Treatment*, *184*(3), 805–816. https://doi.org/10.1007/s10549-020-05908-8

Merino-Barbancho, B., Cipric, A., Arroyo, P., Rujas, M., Gómez del Moral Herranz, R. M., Barev, T., Ciccone, N., & Fico, G. (2025). Methods and computational techniques for predicting adherence to treatment: A scoping review. *Computers in Biology and Medicine*, *192*, 110193. https://doi.org/10.1016/j.compbiomed.2025.110193

Mersha, A. G., Gould, G. S., Bovill, M., & Eftekhari, P. (2020). Barriers and Facilitators of Adherence to Nicotine Replacement Therapy: A Systematic Review and Analysis Using the Capability, Opportunity, Motivation, and Behaviour (COM-B) Model. *International Journal of Environmental Research and Public Health*, *17*(23), Articolo 23. https://doi.org/10.3390/ijerph17238895

Michie, S., Abraham, C., Eccles, M. P., Francis, J. J., Hardeman, W., & Johnston, M. (2011). Strengthening evaluation and implementation by specifying components of behaviour change interventions: A study protocol. *Implementation Science*, *6*(1), 10. https://doi.org/10.1186/1748-5908-6-10

Michie, S., Atkins, L., & West, R. (2014). *The Behaviour Change Wheel: A Guide to Designing Interventions*. Silverback.

Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., Eccles, M. P., Cane, J., & Wood, C. E. (2013). The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International

Consensus for the Reporting of Behavior Change Interventions. *Annals of Behavioral Medicine*, *46*(1), 81–95. https://doi.org/10.1007/s12160-013-9486-6

Michie, S., van Stralen, M. M., & West, R. (2011). The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science: IS*, *6*, 42. https://doi.org/10.1186/1748-5908-6-42

Mishra, P., Vamadevan, A. S., Roy, A., Bhatia, R., Naik, N., Singh, S., Amevinya, G. S., Ampah, E. A., Fernandez, Y., Free, C., Laar, A., Prabhakaran, D., Perel, P., & Legido-Quigley, H. (2021). Exploring Barriers to Medication Adherence Using COM-B Model of Behaviour Among Patients with Cardiovascular Diseases in Low- and Middle-Income Countries: A Qualitative Study. *Patient Preference and Adherence*, *15*, 1359–1371. https://doi.org/10.2147/PPA.S285442

Montagna, E., Palazzo, A., Maisonneuve, P., Cancello, G., Iorfida, M., Sciandivasci, A., Esposito, A., Cardillo, A., Mazza, M., Munzone, E., Lai, A., Goldhirsch, A., & Colleoni, M. (2017). Safety and efficacy study of metronomic vinorelbine, cyclophosphamide plus capecitabine in metastatic breast cancer: A phase II trial. *Cancer Letters*, *400*, 276–281. https://doi.org/10.1016/j.canlet.2017.01.027

Moon, Z. (2017). *Investigating barriers to tamoxifen adherence in women with breast cancer* [King's College London]. https://kclpure.kcl.ac.uk/portal/en/studentTheses/investigating-barriers-to-tamoxifen-adherence-in-women-with-breas

Moon, Z., Moss-Morris, R., Hunter, M. S., Carlisle, S., & Hughes, L. D. (2017). Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: A systematic review. *Patient Preference and Adherence*, *11*, 305–322. https://doi.org/10.2147/PPA.S126651

Moon, Z., Moss-Morris, R., Hunter, M. S., Goodliffe, S., & Hughes, L. D. (2019). Acceptability and feasibility of a self-management intervention for women prescribed tamoxifen. *Health Education Journal*, *78*(8), 901–915. https://doi.org/10.1177/0017896919853856

Moons, K. G. M., Wolff, R. F., Riley, R. D., Whiting, P. F., Westwood, M., Collins, G. S., Reitsma, J. B., Kleijnen, J., & Mallett, S. (2019). PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. *Annals of Internal Medicine*, *170*(1), W1–W33. https://doi.org/10.7326/M18-1377

Mougalian, S. S., Epstein, L. N., Jhaveri, A. P., Han, G., Abu-Khalaf, M., Hofstatter, E. W., DiGiovanna, M. P., Silber, A. L. M., Adelson, K., Pusztai, L., & Gross, C. P. (2017). Bidirectional Text Messaging to Monitor Endocrine Therapy Adherence and Patient-Reported Outcomes in Breast Cancer. *JCO Clinical Cancer Informatics*, *1*, 1–10. https://doi.org/10.1200/CCI.17.00015

Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology*, *18*(1), 143. https://doi.org/10.1186/s12874-018-0611-x

Munro, S., Lewin, S., Swart, T., & Volmink, J. (2007). A review of health behaviour theories: How useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? *BMC Public Health*, *7*(1), 104. https://doi.org/10.1186/1471-2458-7-104

Murphy, C. C., Bartholomew, L. K., Carpentier, M. Y., Bluethmann, S. M., & Vernon, S. W. (2012). Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: A systematic review. *Breast Cancer Research and Treatment*, *134*(2), 459–478. https://doi.org/10.1007/s10549-012-2114-5

Myers, S. A., Weller, S., Schwartz, S., Van Patten, C., LeVasseur, N., Faulkner, G., & Campbell, K. L. (2022). Feasibility of a Supervised Virtual Exercise Program for Women on Hormone Therapy for Breast Cancer. *Translational Journal of the American College of Sports Medicine*, *7*(4), e000213. https://doi.org/10.1249/TJX.0000000000000213

Nabieva, N., & Fasching, P. A. (2021). Endocrine Treatment for Breast Cancer Patients Revisited—History, Standard of Care, and Possibilities of Improvement. *Cancers*, *13*(22), Articolo 22. https://doi.org/10.3390/cancers13225643

Nelson, A. J., Pagidipati, N. J., & Bosworth, H. B. (2024). Improving medication adherence in cardiovascular disease. *Nature Reviews Cardiology*, *21*(6), 417–429. https://doi.org/10.1038/s41569-023-00972-1

Nhean, S., Kostoff, D., Yang, J. J., Vogel, V., & Rybkin, I. I. (2021). Impact of Oral Chemotherapy Management Program on Capecitabine Toxicity Management. *JCO Oncology Practice*, *17*(7), e1021–e1029. https://doi.org/10.1200/OP.20.00947

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., Agoritsas, T., Mistry, N., Iorio, A., Jack, S., Sivaramalingam, B., Iserman, E., Mustafa, R. A., Jedraszewski, D., Cotoi, C., & Haynes, R. B. (2014). Interventions for enhancing medication adherence. *The Cochrane Database of Systematic Reviews*, *2014*(11), CD000011. https://doi.org/10.1002/14651858.CD000011.pub4

Nizet, P., Touchefeu, Y., Pecout, S., Cauchin, E., Beaudouin, E., Mayol, S., Fronteau, C., & Huon, J.-F. (2022). Exploring the factors influencing adherence to oral anticancer drugs in patients with digestive cancer: A qualitative study. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *30*(3), 2591–2604. https://doi.org/10.1007/s00520-021-06663-2

O'Carroll, R. E., Chambers, J. A., Dennis, M., Sudlow, C., & Johnston, M. (2013). Improving Adherence to Medication in Stroke Survivors: A Pilot Randomised Controlled Trial. *Annals of Behavioral Medicine*, *46*(3), 358–368. https://doi.org/10.1007/s12160-013-9515-5

Organisation for Economic Co-operation and Development. (2018, giugno 27). *Investing in medication adherence improves health outcomes and health system efficiency*. OECD. https://www.oecd.org/en/publications/investing-in-medication-adherence-improves-health-outcomes-and-health-system-efficiency_8178962c-en.html

Orrantia-Borunda, E., Anchondo-Nuñez, P., Acuña-Aguilar, L. E., Gómez-Valles, F. O., & Ramírez-Valdespino, C. A. (2022). Subtypes of Breast Cancer. In H. N. Mayrovitz (A c. Di), *Breast Cancer*. Exon Publications. http://www.ncbi.nlm.nih.gov/books/NBK583808/

Osoba, D., Rodrigues, G., Myles, J., Zee, B., & Pater, J. (1998). Interpreting the significance of changes in health-related quality-of-life scores. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *16*(1). https://doi.org/10.1200/JCO.1998.16.1.139

Osterberg, L., & Blaschke, T. (2005). Adherence to Medication. *New England Journal of Medicine*, *353*(5), 487–497. https://doi.org/10.1056/NEJMra050100

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—A web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1), 210. https://doi.org/10.1186/s13643-016-0384-4

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Paladino, A. J., Anderson, J. N., Krukowski, R. A., Waters, T., Kocak, M., Graff, C., Blue, R., Jones, T. N., Buzaglo, J., Vidal, G., Schwartzberg, L., & Graetz, I. (2019). THRIVE study protocol: A randomized controlled trial evaluating a web-based app and tailored messages to improve adherence to adjuvant endocrine therapy among women with breast cancer. *BMC Health Services Research*, *19*(1), 977. https://doi.org/10.1186/s12913-019-4588-x

Panch, T., Mattie, H., & Atun, R. (2019). Artificial intelligence and algorithmic bias: Implications for health systems. *Journal of Global Health*, *9*(2), 020318. https://doi.org/10.7189/jogh.09.020318

Park, H. R., Kang, H. S., Kim, S. H., & Singh-Carlson, S. (2022). Effect of a Smart Pill Bottle Reminder Intervention on Medication Adherence, Self-efficacy, and Depression in Breast Cancer Survivors. *Cancer Nursing*, *45*(6), E874. https://doi.org/10.1097/NCC.0000000000001030

Park, L. G., Ng, F., & Handley, M. A. (2023). The use of the Capability-Opportunity-Motivation Behavior (COM-B) model to identify barriers to medication adherence and the application of mobile health technology in adults with coronary heart disease: A qualitative study. *PEC Innovation*, *3*, 100209. https://doi.org/10.1016/j.pecinn.2023.100209

Peh, K. Q. E., Kwan, Y. H., Goh, H., Ramchandani, H., Phang, J. K., Lim, Z. Y., Loh, D. H. F., Østbye, T., Blalock, D. V., Yoon, S., Bosworth, H. B., Low, L. L., & Thumboo, J. (2021). An Adaptable Framework for Factors Contributing to Medication Adherence: Results from a Systematic Review of 102 Conceptual Frameworks. *Journal of General Internal Medicine*, *36*(9), 2784–2795. https://doi.org/10.1007/s11606-021-06648-1

Penedo, F. J., Oswald, L. B., Kronenfeld, J. P., Garcia, S. F., Cella, D., & Yanez, B. (2020). The increasing value of eHealth in the delivery of patient-centred cancer care. *The Lancet Oncology*, *21*(5), e240–e251. https://doi.org/10.1016/S1470-2045(20)30021-8

Perera, A. I., Thomas, M. G., Moore, J. O., Faasse, K., & Petrie, K. J. (2014). Effect of a Smartphone Application Incorporating Personalized Health-Related Imagery on Adherence to Antiretroviral Therapy: A Randomized Clinical Trial. *AIDS Patient Care and STDs*, *28*(11), 579–586. https://doi.org/10.1089/apc.2014.0156

Pezzolato, M., Marzorati, C., Lanzoni, L., Monzani, D., Masiero, M. A., Pietrobon, R., & Pravettoni, G. (2023). “Interventions to increase adherence to oral therapies in breast cancer patients: A systematic review based on the behavior change technique taxonomy”. *Psycho-Oncology*, *32*(10), 1481–1502. https://doi.org/10.1002/pon.6203

Pezzolato, M., Spada, G. E., Fragale, E., Cutica, I., Masiero, M., Marzorati, C., & Pravettoni, G. (2023). Predictive Models of Psychological Distress, Quality of Life, and Adherence to Medication in Breast Cancer Patients: A Scoping Review. *Patient Preference and Adherence*, *17*, 3461–3473. https://doi.org/10.2147/PPA.S440148

Pezzolato, M., Voskanyan, V., Cutica, I., Marzorati, C., & Pravettoni, G. (2025). *The Use of Artificial Intelligence to Predict and Support Medication Adherence in Breast Cancer Patients: A Systematic Review*. JMIR Preprints. https://doi.org/10.2196/preprints.80128

Pinheiro, L. C., Wheeler, S. B., Reeder-Hayes, K. E., Samuel, C. A., Olshan, A. F., & Reeve, B. B. (2017). Investigating Associations Between Health-Related Quality of Life and Endocrine Therapy Underuse in Women With Early-Stage Breast Cancer. *Journal of Oncology Practice*, *13*(5), e463–e473. https://doi.org/10.1200/JOP.2016.018630

Pistilli, B., Paci, A., Ferreira, A. R., Di Meglio, A., Poinsignon, V., Bardet, A., Menvielle, G., Dumas, A., Pinto, S., Dauchy, S., Fasse, L., Cottu, P. H., Lerebours, F., Coutant, C., Lesur, A., Tredan, O., Soulie, P., Vanlemmens, L., Jouannaud, C., … Vaz-Luis, I. (2020). Serum Detection of Nonadherence to Adjuvant Tamoxifen and Breast Cancer Recurrence Risk. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *38*(24), 2762–2772. https://doi.org/10.1200/JCO.19.01758

Presseau, J., Ivers, N. M., Newham, J. J., Knittle, K., Danko, K. J., & Grimshaw, J. M. (2015). Using a behaviour change techniques taxonomy to identify active ingredients within trials of implementation interventions for diabetes care. *Implementation Science*, *10*(1), 55. https://doi.org/10.1186/s13012-015-0248-7

Prochaska, J. O., & Velicer, W. F. (1997). The transtheoretical model of health behavior change. *American Journal of Health Promotion: AJHP*, *12*(1), 38–48. https://doi.org/10.4278/0890-1171-12.1.38

Qiu, L., Kanski, B., Doerksen, S., Winkels, R., Schmitz, K. H., & Abdullah, S. (2021). Nurse AMIE: Using Smart Speakers to Provide Supportive Care Intervention for Women with Metastatic Breast Cancer. *Extended Abstracts of the 2021 CHI Conference on Human Factors in Computing Systems*, 1–7. https://doi.org/10.1145/3411763.3451827

Ream, M. E., Walsh, E. A., Jacobs, J. M., Taub, C., Lippman, M., Schaefer-Solle, N., Safren, S. A., & Antoni, M. H. (2021). Brief relaxation training is associated with long-term endocrine therapy adherence among women with breast cancer: Post hoc analysis of a randomized controlled trial. *Breast Cancer Research and Treatment*, *190*(1), 79–88. https://doi.org/10.1007/s10549-021-06361-x

Reis, Z. S. N., Pereira, G. M. V., Dias, C. dos S., Lage, E. M., de Oliveira, I. J. R., & Pagano, A. S. (2025). Artificial intelligence-based tools for patient support to enhance medication adherence: A focused review. *Frontiers in Digital Health*, *7*. https://doi.org/10.3389/fdgth.2025.1523070

Rich, A., Brandes, K., Mullan, B., & Hagger, M. S. (2015). Theory of planned behavior and adherence in chronic illness: A meta-analysis. *Journal of Behavioral Medicine*, *38*(4), 673–688. https://doi.org/10.1007/s10865-015-9644-3

Riis, C. L., Jensen, P. T., Bechmann, T., Möller, S., Coulter, A., & Steffensen, K. D. (2020). Satisfaction with care and adherence to treatment when using patient reported outcomes to individualize follow-up care for women with early breast cancer – a pilot randomized controlled trial. *Acta Oncologica*, *59*(4), Articolo 4. https://doi.org/10.1080/0284186X.2020.1717604

Riley, R. D., Ensor, J., Snell, K. I. E., Harrell, F. E., Martin, G. P., Reitsma, J. B., Moons, K. G. M., Collins, G., & van Smeden, M. (2020). Calculating the sample size required for developing a clinical prediction model. *BMJ (Clinical Research Ed.)*, *368*, m441. https://doi.org/10.1136/bmj.m441

Rincon, E., Monteiro-Guerra, F., Rivera-Romero, O., Dorronzoro-Zubiete, E., Sanchez-Bocanegra, C. L., & Gabarron, E. (2017). Mobile Phone Apps for Quality of Life

and Well-Being Assessment in Breast and Prostate Cancer Patients: Systematic Review. *JMIR mHealth and uHealth*, *5*(12), e8741. https://doi.org/10.2196/mhealth.8741

Rinder, P., Marcille, T., Sinel-Boucher, P., Cals-Maurette, M., Kanoun, D., Levy, C., Teixeira, L., Hornus, P., Szeftel, D., & Heudel, P.-E. (2024). Dynamic Projection of Medication Nonpersistence and Nonadherence Among Patients With Early Breast Cancer. *JAMA Network Open*, *7*(5), e2411909. https://doi.org/10.1001/jamanetworkopen.2024.11909

Rosenstock, I. M. (1974). The Health Belief Model and Preventive Health Behavior. *Health Education Monographs*, *2*(4), 354–386. https://doi.org/10.1177/109019817400200405

Safren, S. A., Gonzalez, J. S., & Soroudi, N. (2007). Adherence Training (Life-Steps). In S. A. Safren, J. S. Gonzalez, & N. Soroudi (A c. Di), *Coping with Chronic Illness: A Cognitive-Behavioral Therapy Approach for Adherence and Depression, Therapist Guide* (p. 0). Oxford University Press. https://doi.org/10.1093/med:psych/9780195315165.003.0004

Salama, V., Godinich, B., Geng, Y., Humbert-Vidan, L., Maule, L., Wahid, K. A., Naser, M. A., He, R., Mohamed, A. S. R., Fuller, C. D., & Moreno, A. C. (2024). Artificial Intelligence and Machine Learning in Cancer Pain: A Systematic Review. *Journal of Pain and Symptom Management*, *68*(6), e462–e490. https://doi.org/10.1016/j.jpainsymman.2024.07.025

Salas, M., Mordin, M., Castro, C., Islam, Z., Tu, N., & Hackshaw, M. D. (2022). Health-related quality of life in women with breast cancer: A review of measures. *BMC Cancer*, *22*(1), 66. https://doi.org/10.1186/s12885-021-09157-w

Sanft, T., Harrigan, M., Cartmel, B., Ferrucci, L. M., Li, F.-Y., McGowan, C., Zupa, M., Nguyen, T. H., Ligibel, J., Neuhouser, M. L., Hershman, D. L., Basen-Engquist, K., Jones, B., Knobf, T., Chagpar, A., Silber, A., & Irwin, M. L. (2021). Effect of healthy diet and exercise on chemotherapy completion rate in women with breast

cancer: The Lifestyle, Exercise and Nutrition Early after Diagnosis (LEANer) study: Study protocol for a randomized clinical trial. *Contemporary Clinical Trials*, *109*, 106508. https://doi.org/10.1016/j.cct.2021.106508

Santoleri, F., Lasala, R., Logreco, A., Ranucci, E., & Costantini, A. (2019). Using a treatment diary to improve the medication adherence in patients with chronic myeloid leukaemia. *Journal of Oncology Pharmacy Practice*, *25*(5), 1035–1041. https://doi.org/10.1177/1078155218759184

Schembre, S. M., Liao, Y., Robertson, M. C., Dunton, G. F., Kerr, J., Haffey, M. E., Burnett, T., Basen-Engquist, K., & Hicklen, R. S. (2018). Just-in-Time Feedback in Diet and Physical Activity Interventions: Systematic Review and Practical Design Framework. *Journal of Medical Internet Research*, *20*(3), e8701. https://doi.org/10.2196/jmir.8701

Schofield, W. (1969). The role of psychology in the delivery of health services. *American Psychologist*, *24*(6), 565–584. https://doi.org/10.1037/h0027998

Scott, N. W., Fayers, P., Aaronson, N. K., Bottomley, A., Graeff, A. de, Groenvold, M., Gundy, C., Koller, M., Petersen, M. A., Sprangers, M. A., & Group, E. Q. of L. (2008). *EORTC QLQ-C30 Reference Values Manual*. https://abdn.elsevierpure.com/en/publications/eortc-qlq-c30-reference-values-manual

Seneviratne, M. G., Shah, N. H., & Chu, L. (2020). Bridging the implementation gap of machine learning in healthcare. *BMJ Innovations*, *6*(2). https://doi.org/10.1136/bmjinnov-2019-000359

Shah, K. K., Touchette, D. R., & Marrs, J. C. (2023). Research and scholarly methods: Measuring medication adherence. *JACCP: JOURNAL OF THE AMERICAN COLLEGE OF CLINICAL PHARMACY*, *6*(4), 416–426. https://doi.org/10.1002/jac5.1771

Shah, N. H., Milstein, A., & Bagley, P., Steven C. (2019). Making Machine Learning Models Clinically Useful. *JAMA*, *322*(14), 1351–1352.

https://doi.org/10.1001/jama.2019.10306

Sheikh, H., Prins, C., & Schrijvers, E. (2023). Artificial Intelligence: Definition and Background. In H. Sheikh, C. Prins, & E. Schrijvers, *Mission AI* (pp. 15–41). Springer International Publishing. https://doi.org/10.1007/978-3-031-21448-6_2

Shelby, R. A., Dorfman, C. S., Bosworth, H. B., Keefe, F., Sutton, L., Owen, L., Corsino, L., Erkanli, A., Reed, S. D., Arthur, S. S., Somers, T., Barrett, N., Huettel, S., Gonzalez, J. M., & Kimmick, G. (2019). Testing a behavioral intervention to improve adherence to adjuvant endocrine therapy (AET). *Contemporary Clinical Trials*, *76*, 120–131. https://doi.org/10.1016/j.cct.2018.11.010

Shinn, E. H., Busch, B. E., Jasemi, N., Lyman, C. A., Toole, J. T., Richman, S. C., Symmans, W. F., Chavez-MacGregor, M., Peterson, S. K., & Broderick, G. (2022). Network Modeling of Complex Time-Dependent Changes in Patient Adherence to Adjuvant Endocrine Treatment in ER+ Breast Cancer. *Frontiers in Psychology*, *13*, 856813. https://doi.org/10.3389/fpsyg.2022.856813

Silverman, S. R., Schertz, L. A., Yuen, H. K., Lowman, J. D., & Bickel, C. S. (2012). Systematic review of the methodological quality and outcome measures utilized in exercise interventions for adults with spinal cord injury. *Spinal Cord*, *50*(10), 718–727. https://doi.org/10.1038/sc.2012.78

Skrabal Ross, X., Gunn, K. M., Suppiah, V., Patterson, P., & Olver, I. (2020). A review of factors influencing non-adherence to oral antineoplastic drugs. *Supportive Care in Cancer*, *28*(9), 4043–4050. https://doi.org/10.1007/s00520-020-05469-y

S.Lewis-Beck, M., Bryman, A., & Liao, T. F. (2004). Social Desirability Bias. In *The SAGE Encyclopedia of Social Science Research Methods* (pp. 1045–1045). Sage Publications, Inc. https://doi.org/10.4135/9781412950589

Sliwoski, G., Kothiwale, S., Meiler, J., & Lowe, E. W. (2014). Computational Methods in Drug Discovery. *Pharmacological Reviews*, *66*(1), 334–395. https://doi.org/10.1124/pr.112.007336

Smith, S. G., Ellison, R., Hall, L., Clark, J., Hartley, S., Mason, E., Metherell, J., Olivier, C., Napp, V., Naik, J., Buckley, S., Hirst, C., Hartup, S., Neal, R. D., Velikova, G., Farrin, A., Collinson, M., & Graham, C. D. (2022). Acceptance and Commitment Therapy to support medication decision-making and quality of life in women with breast cancer: Protocol for a pilot randomised controlled trial. *Pilot and Feasibility Studies*, *8*(1), 33. https://doi.org/10.1186/s40814-022-00985-6

Smith, S. G., Green, S. M. C., Ellison, R., Foy, R., Graham, C. D., Mason, E., French, D. P., Hall, L. H., Wilkes, H., McNaught, E., Raine, E., Walwyn, R., Howdon, D., Clark, J., Rousseau, N., Buxton, J., Moore, S. J. L., Parbutt, C., Velikova, G., … Collinson, M. (2023). Refining and optimising a behavioural intervention to support endocrine therapy adherence (ROSETA) in UK women with breast cancer: Protocol for a pilot fractional factorial trial. *BMJ Open*, *13*(2), e069971. https://doi.org/10.1136/bmjopen-2022-069971

Snow, G. (2013). *blockrand: Randomization for Block Random Clinical Trials* (Versione R package version 1.3) [Software]. http://CRAN.R-project.org/package=blockrand

Sprangers, M. A., Groenvold, M., Arraras, J. I., Franklin, J., te Velde, A., Muller, M., Franzini, L., Williams, A., de Haes, H. C., Hopwood, P., Cull, A., & Aaronson, N. K. (1996). The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: First results from a three-country field study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *14*(10), 2756–2768. https://doi.org/10.1200/JCO.1996.14.10.2756

Steele, C. M. (1988). The Psychology of Self-Affirmation: Sustaining the Integrity of the Self. In L. Berkowitz (A c. Di), *Advances in Experimental Social Psychology* (Vol. 21, pp. 261–302). Academic Press. https://doi.org/10.1016/S0065-2601(08)60229-4

Talat, U., Schmidtke, K. A., Khanal, S., Chan, A., Turner, A., Horne, R., Chadborn, T., Gold, N., Sallis, A., & Vlaev, I. (2022). A Systematic Review of Nudge

Interventions to Optimize Medication Prescribing. *Frontiers in Pharmacology*, *13*, 798916. https://doi.org/10.3389/fphar.2022.798916

Tan, E. H., Wong, A. L. A., Tan, C. C., Wong, P., Tan, S. H., Ang, L. E. Y., Lim, S. E., Chong, W. Q., Ho, J., Lee, S. C., & Tai, B. C. (2020). Improving medication adherence with adjuvant aromatase inhibitor in women with breast cancer: A randomised controlled trial to evaluate the effect of short message service (SMS) reminder. *The Breast*, *53*, 77–84. https://doi.org/10.1016/j.breast.2020.06.012

Teo, V., Weinman, J., & Yap, K. Z. (2025). Best fit framework synthesis of qualitative studies on factors associated with medication nonadherence in people with type 2 diabetes using the COM-B model. *British Journal of Clinical Pharmacology*, *91*(6), 1675–1691. https://doi.org/10.1111/bcp.70059

Thrift-Perry, M., Cabanes, A., Cardoso, F., Hunt, K. M., Cruz, T. A., & Faircloth, K. (2018). Global analysis of metastatic breast cancer policy gaps and advocacy efforts across the patient journey. *The Breast*, *41*, 93–106. https://doi.org/10.1016/j.breast.2018.06.005

Todd, A., Waldron, C., McGeagh, L., Norris, R., Bolnykh, I., Stewart, S. J., Slodkowska-Barabasz, J., Moon, Z., Cahir, C., Thompson, S., Harmer, V., Wells, M., Watson, E., Sharp, L., & Team, the S. R. (2024). Identifying determinants of adherence to adjuvant endocrine therapy following breast cancer: A systematic review of reviews. *Cancer Medicine*, *13*(3), e6937. https://doi.org/10.1002/cam4.6937

Toma, M., & Wei, O. C. (2023). Predictive Modeling in Medicine. *Encyclopedia*, *3*(2), Articolo 2. https://doi.org/10.3390/encyclopedia3020042

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Tsegaye, B., Snell, K. I. E., Archer, L., Kirtley, S., Riley, R. D., Sperrin, M., Van Calster, B., Collins, G. S., & Dhiman, P. (2025). Larger sample sizes are needed when developing a clinical prediction model using machine learning in oncology: Methodological systematic review. *Journal of Clinical Epidemiology*, *180*, 111675. https://doi.org/10.1016/j.jclinepi.2025.111675

Uchikov, P., Khalid, U., Dedaj-Salad, G. H., Ghale, D., Rajadurai, H., Kraeva, M., Kraev, K., Hristov, B., Doykov, M., Mitova, V., Bozhkova, M., Markov, S., & Stanchev, P. (2024). Artificial Intelligence in Breast Cancer Diagnosis and Treatment: Advances in Imaging, Pathology, and Personalized Care. *Life*, *14*(11), Articolo 11. https://doi.org/10.3390/life14111451

U.S. Food and Drug Administration. (2017). *Software as a Medical Device (SAMD): Clinical Evaluation*. FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/software-medical-device-samd-clinical-evaluation

Valerio, M. R., Spadaro, P., Arcanà, C., Borsellino, N., Cipolla, C., Vigneri, P., Piazza, D., & Gebbia, V. (2021). Oral Vinorelbine and Capecitabine as First-Line Therapy in Metastatic Breast Cancer: A Retrospective Analysis. *Future Science OA*, *7*(10), FSO750. https://doi.org/10.2144/fsoa-2020-0095

Varga, T. V., Niss, K., Estampador, A. C., Collin, C. B., & Moseley, P. L. (2020). Association is not prediction: A landscape of confused reporting in diabetes – A systematic review. *Diabetes Research and Clinical Practice*, *170*, 108497. https://doi.org/10.1016/j.diabres.2020.108497

Vinogradov, R., Holden, E., Patel, M., Grigg, R., Errington, L., Araújo-Soares, V., & Rankin, J. (2024). Barriers and facilitators of adherence to low-dose aspirin during pregnancy: A co-produced systematic review and COM-B framework synthesis of qualitative evidence. *PLOS ONE*, *19*(5), e0302720. https://doi.org/10.1371/journal.pone.0302720

von Blanckenburg, P., Schuricht, F., Albert, U.-S., Rief, W., & Nestoriuc, Y. (2013). Optimizing expectations to prevent side effects and enhance quality of life in breast

cancer patients undergoing endocrine therapy: Study protocol of a randomized controlled trial. *BMC Cancer, 13*(1), 426. https://doi.org/10.1186/1471-2407-13-426

Wagner, V. L., Jing, W., Boscoe, F. P., Schymura, M. J., Roohan, P. J., & Gesten, F. C. (2016). Improving Adjuvant Hormone Therapy Use in Medicaid Managed Care-Insured Women, New York State, 2012-2014. *Preventing Chronic Disease, 13*, E120. https://doi.org/10.5888/pcd13.160185

Waks, A. G., & Winer, E. P. (2019). Breast Cancer Treatment: A Review. *JAMA*, *321*(3), 288–300. https://doi.org/10.1001/jama.2018.19323

Wang, Y.-P., & Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: A comprehensive review. *Brazilian Journal of Psychiatry*, *35*, 416–431. https://doi.org/10.1590/1516-4446-2012-1048

Watson, J., Hutyra, C. A., Clancy, S. M., Chandiramani, A., Bedoya, A., Ilangovan, K., Nderitu, N., & Poon, E. G. (2020). Overcoming barriers to the adoption and implementation of predictive modeling and machine learning in clinical care: What can we learn from US academic medical centers? *JAMIA Open*, *3*(2), 167–172. https://doi.org/10.1093/jamiaopen/ooz046

Weinman, J., Ali, I., Hodgkinson, A., Canfield, M., & Jackson, C. (2019). Pilot Testing Of A Brief Pre-Consultation Screener For Improving The Identification And Discussion Of Medication Adherence In Routine Consultations. *Patient Preference and Adherence*, *13*, 1895–1898. https://doi.org/10.2147/PPA.S219860

Wessler, B. S., Lana Lai, Y., Kramer, W., Cangelosi, M., Raman, G., Lutz, J. S., & Kent, D. M. (2015). Clinical Prediction Models for Cardiovascular Disease: The Tufts PACE CPM Database. *Circulation. Cardiovascular quality and outcomes*, *8*(4), 368–375. https://doi.org/10.1161/CIRCOUTCOMES.115.001693

Wilhelmsen, N. C., & Eriksson, T. (2019). Medication adherence interventions and outcomes: An overview of systematic reviews. *European Journal of Hospital*

Pharmacy: Science and Practice, *26*(4), 187–192. https://doi.org/10.1136/ejhpharm-2018-001725

Williams, D. M., Rhodes, R. E., & Conner, M. T. (2019). Conceptualizing and intervening on affective determinants of health behaviour. *Psychology & Health*. https://www.tandfonline.com/doi/abs/10.1080/08870446.2019.1675659

Williamson, S. M., & Prybutok, V. (2024). Balancing Privacy and Progress: A Review of Privacy Challenges, Systemic Oversight, and Patient Perceptions in AI-Driven Healthcare. *Applied Sciences*, *14*(2), Articolo 2. https://doi.org/10.3390/app14020675

Wong, W. M., Chan, D. N. S., He, X., & So, W. K. W. (2023). Effectiveness of Pharmacological and Nonpharmacological Interventions for Managing the Fatigue–Sleep Disturbance–Depression Symptom Cluster in Breast Cancer Patients Undergoing Chemotherapy: A Systematic Review. *Cancer Nursing*, *46*(2), E70. https://doi.org/10.1097/NCC.0000000000001048

World Health Organization. (2003). *Adherence to long-term therapies: Evidence for action*. World Health Organization. https://iris.who.int/handle/10665/42682

Wouters, O. J., & Kesselheim, A. S. (2024). Quantifying Research and Development Expenditures in the Drug Industry. *JAMA Network Open*, *7*(6), e2415407. https://doi.org/10.1001/jamanetworkopen.2024.15407

Wright, C., Barnett, A., Campbell, K. L., Kelly, J. T., & Hamilton, K. (2022). Behaviour change theories and techniques used to inform nutrition interventions for adults undergoing bariatric surgery: A systematic review. *Nutrition & Dietetics*, *79*(1), 110–128. https://doi.org/10.1111/1747-0080.12728

Wu, Z., Xia, F., & Lin, R. (2024). Global burden of cancer and associated risk factors in 204 countries and territories, 1980–2021: A systematic analysis for the GBD 2021. *Journal of Hematology & Oncology*, *17*(1), 119. https://doi.org/10.1186/s13045-024-01640-8

Xiong, X., Zheng, L.-W., Ding, Y., Chen, Y.-F., Cai, Y.-W., Wang, L.-P., Huang, L., Liu, C.-C., Shao, Z.-M., & Yu, K.-D. (2025). Breast cancer: Pathogenesis and treatments. *Signal Transduction and Targeted Therapy*, *10*(1), 1–33. https://doi.org/10.1038/s41392-024-02108-4

Xu, L., Sanders, L., Li, K., & Chow, J. C. L. (2021). Chatbot for Health Care and Oncology Applications Using Artificial Intelligence and Machine Learning: Systematic Review. *JMIR Cancer*, *7*(4), e27850. https://doi.org/10.2196/27850

Yanez, B., Gray, R. J., Sparano, J. A., Carlos, R. C., Sadigh, G., Garcia, S. F., Gareen, I. F., Whelan, T. J., Sledge, G. W., Cella, D., & Wagner, L. I. (2021). Association of Modifiable Risk Factors With Early Discontinuation of Adjuvant Endocrine Therapy: A Post Hoc Analysis of a Randomized Clinical Trial. *JAMA Oncology*, *7*(8), 1196–1202. https://doi.org/10.1001/jamaoncol.2021.1693

Yanez, B., Oswald, L. B., Van Denburg, A. N., Baik, S. H., Czech, K. A., Buitrago, D., Maletich, C., Wortman, K., Penedo, F. J., & Victorson, D. E. (2022). Rationale and usability findings of an e-health intervention to improve oral anticancer adherence among breast cancer survivors: The My Journey mindfulness study. *Contemporary Clinical Trials Communications*, *26*, 100898. https://doi.org/10.1016/j.conctc.2022.100898

Yang, S.-R., Chien, J.-T., & Lee, C.-Y. (2025). Advancements in Clinical Evaluation and Regulatory Frameworks for AI-Driven Software as a Medical Device (SaMD). *IEEE Open Journal of Engineering in Medicine and Biology*, *6*, 147–151. https://doi.org/10.1109/OJEMB.2024.3485534

Yerrapragada, G., Siadimas, A., Babaeian, A., Sharma, V., & O'Neill, T. J. (2021). Machine Learning to Predict Tamoxifen Nonadherence Among US Commercially Insured Patients With Metastatic Breast Cancer. *JCO Clinical Cancer Informatics*, *5*, 814–825. https://doi.org/10.1200/CCI.20.00102

Yu, J., Wu, J., Huang, O., Chen, X., & Shen, K. (2021). A Smartphone-Based App to Improve Adjuvant Treatment Adherence to Multidisciplinary Decisions in Patients

With Early-Stage Breast Cancer: Observational Study. *Journal of Medical Internet Research*, *23*(9), e27576. https://doi.org/10.2196/27576

Yu, K.-D., Zhou, Y., Liu, G.-Y., Li, B., He, P.-Q., Zhang, H.-W., Lou, L.-H., Wang, X.-J., Wang, S., Tang, J.-H., Liu, Y.-H., Wang, X., Jiang, Z.-F., Ma, L.-W., Gu, L., Cao, M.-Z., Zhang, Q.-Y., Wang, S.-M., Su, F.-X., … Shen, Z.-Z. (2012). A prospective, multicenter, controlled, observational study to evaluate the efficacy of a patient support program in improving patients' persistence to adjuvant aromatase inhibitor medication for postmenopausal, early stage breast cancer. *Breast Cancer Research and Treatment*, *134*(1), 307–313. https://doi.org/10.1007/s10549-012-2059-8

Yu, P., Xu, H., Hu, X., & Deng, C. (2023). Leveraging Generative AI and Large Language Models: A Comprehensive Roadmap for Healthcare Integration. *Healthcare*, *11*(20), Articolo 20. https://doi.org/10.3390/healthcare11202776

Yung, A., Kay, J., Beale, P., Gibson, K. A., & Shaw, T. (2021). Computer-Based Decision Tools for Shared Therapeutic Decision-making in Oncology: Systematic Review. *JMIR Cancer*, *7*(4), e31616. https://doi.org/10.2196/31616

Yussof, I., Mohd Tahir, N. A., Hatah, E., & Mohamed Shah, N. (2022). Factors influencing five-year adherence to adjuvant endocrine therapy in breast cancer patients: A systematic review. *Breast (Edinburgh, Scotland)*, *62*, 22–35. https://doi.org/10.1016/j.breast.2022.01.012

Zhang, B., Shi, H., & Wang, H. (2023). Machine Learning and AI in Cancer Prognosis, Prediction, and Treatment Selection: A Critical Approach. *Journal of Multidisciplinary Healthcare*, *16*, 1779–1791. https://doi.org/10.2147/JMDH.S410301

Zhou, B., Yang, G., Shi, Z., & Ma, S. (2022). Natural Language Processing for Smart Healthcare. *IEEE Reviews in Biomedical Engineering*, *17*, 4–18. https://doi.org/10.1109/RBME.2022.3210270

Ziller, V., Kyvernitakis, I., Knöll, D., Storch, A., Hars, O., & Hadji, P. (2013). Influence of a patient information program on adherence and persistence with an aromatase

inhibitor in breast cancer treatment—The COMPAS study. *BMC Cancer*, *13*(1), 407. https://doi.org/10.1186/1471-2407-13-407