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Review

EBCC-14 manifesto: Addressing disparities in access to innovation for patients with metastatic breast cancer across Europe

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ABSTRACT

The European Breast Cancer Council (EBCC) traditionally identifies controversies or major deficiencies in the management of patients with breast cancer and selects a multidisciplinary expert team to collaborate in setting crucial principles and recommendations to improve breast cancer care. The 2024 EBCC manifesto focuses on disparities in the care of patients with metastatic breast cancer. There are several reasons for existing disparities both between and within countries. Our recommendations aim to address the stigma of metastatic disease, which has led to significant disparities in access to innovative care regardless of the gross national income of a country. These recommendations are for different stakeholders to promote the care of patients with metastatic breast cancer across Europe and worldwide.

1. Introduction

The European Breast Cancer Council (EBCC) aims to promote the high-quality evidence-based care of all patients with breast cancer. Each year, the EBCC manifesto identifies crucial topics that need to be addressed, taking into account differences across European countries. [1–4] The EBCC-14 manifesto focuses on disparities in the care of patients with metastatic breast cancer (mBC).

Inequitable access to healthcare for breast cancer has long been recognised [5–11]. In 2024, disparities in access to healthcare persist

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and continue to widen in some countries, due in large part to challenges in accessing new effective therapies and cancer services and a lack of political will to implement effective public health policies [12–14]. Gross national income is a major factor that drives these disparities [15,16], and the inadequate care of patients with cancer may result in financial toxicity, creating a vicious cycle for national economics. One-third of people with a cancer diagnosis will permanently give up work and about half will experience income loss; the diagnosis results in financial distress in up to two-thirds of patients [17]. Financial toxicity varies significantly between countries, but demographic and individual socioeconomic factors within a country play a role and younger, unemployed and divorced patients with children are particularly vulnerable to financial toxicity.

While economic disparities and a country's gross national income are frequently cited as barriers to innovative therapies, they represent only two of several factors contributing to unequal access [18,19]. Among the underserved populations are those with lower socioeconomic status, those with a lower education level, people living in rural areas and migrants [20]. Lower socioeconomic status is associated with a lower incidence but higher lethality of breast cancer in Europe [21]. Furthermore, disparities in care are not limited to access to innovative therapies: a recent EUROPA DONNA survey revealed variable and limited access to psycho-oncology, physiotherapy, nutritional services and coordinated care [11], which are basic needs for patients diagnosed with cancer or any chronic disease.

We must be less fatalistic and more optimistic about the trajectory of mBC while remaining realistic about what we can do to improve the care, support and dignity of people living with mBC and to ensure continued investment in their wellbeing. In this article, we identify those innovations that bring the greatest benefit but are not equally accessible, highlight barriers to accessing innovation and propose steps towards improved access to innovation. Our goal is to improve outcomes for patients with mBC by levelling up major disparities between and within countries in Europe, and between mBC and early breast cancer (eBC). Several initiatives are already ongoing but much more can be achieved. Although the EBCC, which comprises clinicians and patients living with or after breast cancer, has neither the mandate nor the powers to implement actionable steps, this manifesto aims to reinforce and complement existing efforts. It may be used to support advocacy for policies at both national and European levels and is divided into five broad categories: stigma, registries and real-world data, multidisciplinary care, clinical research and quality indicators.

2. Living with the stigma of mBC

mBC is a diverse disease encompassing a spectrum ranging from potentially curative oligometastatic disease to a dismal prognosis with no effective treatments and very short life expectancy [22]. Consequently, the needs of patients with mBC are heterogeneous and often differ substantially from those of patients with eBC [23]. Many people living with mBC face long-term incurable disease and chronic treatment, which may include multiple lines of therapy, all with different side effects.

Although public perception has advanced, cancer is still surrounded by stigma, taboo and euphemism, which affects ethnic minorities disproportionately [24]. One in 10 respondents to a UK survey indicated they would find it difficult being around someone with cancer and a similar proportion said they would find it difficult to talk to someone with cancer [24]. The stigma and fatalistic view of mBC may prevent some individuals from seeking advice, information or medical care. Many patients and their families cope with stigma through non-disclosure, exacerbating difficulties in accessing support [25]. Family worries bring an additional emotional burden and most young adults with cancer are worried about their family's financial situation [26]. Following a diagnosis of advanced cancer, a reduced ability to work and lower income are coupled with increased treatment-related expenses (direct and indirect), combining to place a substantial financial burden on patients [17,27].

Compared with individuals diagnosed with eBC, patients with mBC have reported a sense of abandonment and neglect [25,28,29]. Psychological and emotional support provision are often tailored towards eBC rather than mBC [28]. People with mBC are frequently undervalued, under-recognised and under-represented [30] but want to be counted, seen, supported and treated. In some countries, politicians may neglect the benefit of prolonging the lives of people with mBC, preferring to invest in eBC [11,31].

To overcome such stigma, the public, policy makers and healthcare providers need to recognise that mBC is not synonymous with imminent death and that people with mBC deserve the same opportunities and rights as everyone else. We should ensure that individuals with mBC can continue with their important contributions to society, including family, community, science, the arts, journalism and activism. The prognosis for people with mBC has improved dramatically in recent years, and it is not uncommon for people to live with mBC for 10 years [32,33]. Society needs to know this, accept this and be able to fully support patients and their caregivers. Furthermore, as breast cancer is so prevalent and treatments are improving, the number of people living with mBC is likely to continue growing and all should be well cared for and encouraged to continue to be a productive part of society.

Several powerful campaigns are raising public awareness of mBC, including those by EUROPA DONNA [34] and the Advanced Breast Cancer (ABC) Global Alliance [35]. Investment in public education is critical to disseminate information to the broadest possible audience, raise awareness of the important contribution of people with mBC, and recognise the impact on those surrounding and supporting people living with mBC, particularly when resources are limited. Ongoing initiatives to ensure that the specific needs of patients with mBC receive the attention they deserve include the Lancet Breast Cancer Commission [29,36], Europe's Beating Cancer Plan [37] and the ABC Global Alliance [28]. These initiatives strive to change the collective mentality towards mBC to be more optimistic, and to recognise the very different challenges experienced and care provision needed by people living with mBC compared with eBC.

Receiving healthcare for mBC can become a full-time job [35,38,39]. Nevertheless, many people with mBC need or want to continue working, perhaps because the workplace provides them with a sense of normality and purpose. The challenges associated with the emotional, physical and cognitive changes brought about by mBC are often poorly understood and should be addressed [28]. Changing labour laws to allow people with mBC to continue working in a more flexible way according to their altered physical and psychological capacity, with compensation to the individuals and the employers, would bring cost savings benefitting both governments and society, as well as reducing the stigma of mBC and improving individuals' self-esteem [40].

The stigma associated with a diagnosis of mBC extends beyond the general public to the healthcare profession [25]. Denying intensive care units to people with advanced cancer during the COVID-19 pandemic is an example of the discrimination against people living with advanced cancer [41,42].

The stigma of metastatic disease should not guide social-clinical management. Patients with mBC deserve the best possible care, regardless of their prognosis, to enhance survival outcomes and quality of life (QoL). All patients should have access to appropriate support (medical, social, psychological, workplace) and supportive care throughout their mBC [19]. Future policies should focus on survivorship (including mental, psychosocial and nutritional support) across healthcare systems [43–46]. As disease progresses, patients deserve optimal end-of-life care and their caregivers deserve psychosocial support.

Recommendation 1. Increase the visibility of mBC to society and facilitate the involvement of people with mBC in trials, the workplace and everyday life as much as they want and are able.

3. Registries and real-world data

One of the first challenges when trying to redress inequity in mBC is the unknown prevalence of mBC in many countries [47]. Few countries have registries of patients living with mBC: some record breast cancer diagnoses but do not differentiate between eBC and mBC [29,48] and others have no registries [11]. This lack of information limits our ability to identify unequal access to innovation for mBC and allocate resources appropriately. Furthermore, the content structure of existing databases makes comparison between countries difficult [49], and lack of information on social factors and demographics, including ethnicity, hampers attempts to identify and address disparities [50]. Therefore, collection of a defined set of data, with minimal requirements aligned internationally, is critical. Analyses by the International Cancer Benchmarking Partnership illustrate the value of such efforts in identifying and understanding disparities [51]. Recently updated recommendations for standardised data collection in European registries aim to facilitate comparison and integration of databases [49]; sharing national registries globally is critical to obtaining reliable data [52]. Furthermore, policies and legal frameworks need to allow interconnection and data sharing between registries. There is a balance between data protection and patients' wishes to be heard and recognised; therefore, legal exceptions to data protection should be considered openly and proactively [52]. Cross-referencing between registries of chemotherapy administration and cancer would require policy makers to respond to calls for a waiver to data protection laws.

Recommendation 2. Implement a national cancer registry recording stage at diagnosis and relapses in every European country and share with the International Agency for Research on Cancer (IARC) to understand how many people are living with mBC.

Some countries have registries that provide a rich resource for analysing access and outcomes, including The Netherlands Cancer Registry [53–57], the SONABRE registry (also in The Netherlands) [32,58–60], the French Epidemiological Strategy and Medical Economics (ESME) programme [61–65], the German Centre for Cancer Registry Data [66], the Belgian Cancer Registry [67], the Swedish Cancer Registry [68] and the Association of Nordic Cancer Registries (NORDCAN) database [69]. The power of such registries is exemplified by the experience in New Zealand. Analysis of mBC registry data demonstrated that the life expectancy of people with mBC in New Zealand was half that of patients in Australia; that patients received a median of only one treatment line for mBC; and that empirical (or no) treatment was offered to many patients. There was very little investment in treatment for mBC, no treatment guidelines and a perception that access to treatment was less important because patients were incurable. These findings provided the impetus for dramatic changes within the entire oncology community to improve access and outcomes and new investments [31].

As well as identifying disparities in care, real-world data can demonstrate the benefit of best-quality care, potentially supporting reimbursement decisions and filling evidence gaps that cannot be addressed through clinical trials. As many reimbursement decisions are taken nationally, the generalisability of data from one country may not be acceptable to decision makers and policy drivers in another; however, the impact of differences in the availability and access to best possible care can be compared between countries if real-world data are collected nationwide. Standardising real-world data reporting is encouraged, for both registries and hospitals [70,71], and efforts are underway for Europe-wide coordination [72–74].

Recommendation 3. Harmonise, monitor and use routinely collected real-world and registry data (including but not limited to details of biomarker/genetic testing, treatment and quality of life) to support reimbursement policies and improve access to treatment, trials and services and to evaluate outcomes.

4. Multidisciplinary care

4.1. Ensure equal access to high-quality multidisciplinary care

There are several reasons why high-quality multidisciplinary care is denied, including: financial/insurance and reimbursement policies [3,11,28,29,75], indirect costs, geographical variations (with less access in rural or underserved areas [11,29,76]), socioeconomic inequities [29], limited healthcare resources/bottlenecks, frailty and geriatric assessment and disparity in regulatory approval. These inequalities exist at all stages of mBC care.

4.2. Ensure timely referral to a multidisciplinary specialist care pathway

Detection and treatment of breast cancer at an early stage reduce inequalities in breast cancer outcomes [77]. Improved screening and earlier detection also result in a change in the profile of patients presenting with de novo mBC [78]. In Europe, the proportion of patients with a first diagnosis of mBC has decreased in the past two decades but, in most European countries, older patients and those with the lowest socioeconomic status are more likely to present with de novo mBC [79]. Globally, women in rural areas are more likely to be diagnosed at a later stage than those in urban areas [80–82].

Once diagnosed, all patients with mBC should be managed at a specialist centre by a multidisciplinary team (MDT) of experts relevant to their individual situation [2]. Multidisciplinary care improves outcomes in breast cancer [2,83,84], whereas treatment in non-specialist centres has a detrimental effect [2,85]. MDT implementation must be optimised to ensure that all patients are reviewed and discussed [2,86,87]. MDTs were the focus of a previous EBCC manifesto [2] and are not discussed in detail here; however, it is worth highlighting that MDT discussion increases the likelihood of a patient participating in a clinical trial (discussed in Section 4). In addition, molecular tumour boards are increasingly important, with more personalised treatment options requiring molecular testing as well as pathology [88,89]. Although more complex and expensive than conventional MDTs, the ability of molecular tumour boards to improve patient selection for targeted therapies may provide more cost-effective care and improved access to clinical trials [90,91]. Importantly, MDT care via a specialist centre does not preclude delivery of (systemic) treatment closer to home, which can lessen the burden of treatment on patients' quality of life. This can often be achieved through virtual meetings, networks and satellite centres, allowing optimal discussion and involvement of all specialists.

Most recent innovations in systemic therapy for mBC involve targeted treatments, many of which have demonstrated efficacy in biomarker- or molecularly selected subtypes of mBC. A comprehensive workup to determine the most appropriate management of an individual with mBC is therefore critical and requires high-quality timely imaging and biomarker testing backed by adequate reimbursement and up-to-date guidance to clinicians [8,89,92–94]. Diagnostic tests have been reported to account for less than 2 % of total healthcare spending but to influence 60 % of clinical decision making [89,95].

The diagnosis of mBC requires the demonstration or confirmation that metastatic tissue is present in a specific organ by means of imaging. Besides considerations of diagnostic effectiveness, the choice of imaging modality may vary according to local availability, adherence to guidelines or consideration of innovative therapeutic approaches. Although still often recommended in guidelines, standard imaging modalities (bone scintigraphy, computed tomography), may not be sufficient for an early diagnosis of metastasis. Modern ("next-generation") imaging modalities (18-fluoro-deoxyglucose positron emission tomography [FDG-PET]/computed tomography and whole-body magnetic resonance imaging) allow reliable diagnosis of oligometastasis, consideration of metastasis-directed treatments and subsequent evaluation of the response to treatment [96]. The potential to offer patients the most innovative therapeutic approaches and/or enrolment in trials assumes

the availability of these modern imaging modalities [97]. These modern imaging methods should be available for all patients in whom they are recommended according to guidelines.

At mBC diagnosis, a metastatic site should be biopsied under imaging guidance to exclude a benign lesion or metastasis from a different cancer and to lessen the risk of treating the 'wrong' phenotype [93,98–101]. Biomarkers (hormonal, molecular and gene expression) in primary versus metastatic samples are often discordant, affecting therapeutic targets and treatment selection [102–105].

Despite existing guidelines for biomarker testing to select patients for evidence-based therapeutic options [93,106,107], disparities in essential pathology/biomarker testing remain [108]. Access to genetic testing is variable [89,109], and some patients are required to pay through out-of-pocket funding or private insurance [11,108]. In some cases patients have to request genomic tests, which requires patient awareness and education on testing [11]. A recent study demonstrated that at least one genomic drug target with high-level evidence can be identified with next-generation sequencing in more than half of patients with mBC [105].

Barriers to the use of essential and innovative diagnostic tests include outdated regulations, inadequate infrastructure for data collection and laboratory analysis, insufficient training and fragmented approval and funding systems [89]. Uptake of genomic testing may depend on the likelihood of identifying an actionable target and the availability of a treatment targeting the identified biomarker, as well as turnaround times and cost [110,111]. Tackling access to biomolecular technologies is a critical step in reducing inequalities with respect to precision medicine for cancer [111]. Digital pathways to overcome resource shortages and bottlenecks for appointment-based genetic testing and counselling have shown high patient and healthcare professional acceptability and may broaden access [112].

A recent survey of biomarker testing in Europe indicated that access to single biomarker tests was lower in countries that lacked diagnostic laboratory infrastructure (including several Eastern and Central European countries), had inefficient organisation of diagnostic laboratory infrastructure and/or inadequate public reimbursement of testing, and where pharmaceutical companies and patients pay for testing [94]. In Central and Eastern European countries, limited reimbursement is a significant barrier to molecular testing [113]. Uptake of multigene testing (e.g. next-generation sequencing) is even more variable, and advanced biomolecular technologies are inaccessible in many countries [111]. Furthermore, the problem of access to diagnostic tests varies within as well as between countries. In Western and Northern Europe more than 90 % of laboratories participate in quality assurance schemes, but the percentage is lower elsewhere [94]. If quality assurance is lacking, test results are less reliable and physicians and patients may have little confidence in using them to make treatment decisions. Without action, the problem of access to biomarker testing is likely to worsen with the increasing number of tumour-agnostic therapies relying solely on molecular markers to define eligibility [114].

Increasingly, liquid biopsy is playing an important role in diagnostics and workup [115] but there are several barriers to its uptake, not least the expense and complexity of implementation [88,116]. Equal access to high-quality and timely biomarker testing of mBC, backed by adequate reimbursement and up-to-date guidance to clinicians, is a priority.

4.3. Ensure the availability of best standard-of-care management, including innovative treatments and long-term support

If enrolment in a clinical trial is not an option or is not in an individual's best interests, all Europeans with mBC should have timely access to best standard-of-care management. Numerous treatment advances have improved outcomes for patients with mBC [19,93]; however, disparities in timely access to these developments result in inequitable outcomes. Geographical variations are seen in access to standard care, even within countries, and specific patient groups, such as older patients, may be less likely to receive innovative care [117]. Significant improvements in radiation therapy techniques (e.g. hypofractionation and stereotactic radiation therapy) reduce toxicity and treatment burden and may improve QoL [118–120]. Optimal modern personalised radiation therapy options should be offered to all patients with mBC, across the spectrum of disease.

Delaying palliative radiation therapy adversely affects QoL and overall survival. Early integration of specialist palliative (or supportive) care to manage symptoms, pain and QoL improves outcomes for patients with advanced cancer [121–124]. Supervised physical exercise appears to improve mental wellbeing and physical fitness and reduce fatigue and pain in patients with mBC, highlighting the importance of holistic care [125]. Specialist palliative care can improve patient and caregiver satisfaction and reduce the amount of time spent in acute hospital settings [126]. However, inpatient palliative care is often provided only in the final month of life, and (outside large cancer centres) is delivered less frequently to older than younger patients [127].

4.4. Equitable access and sustainable funding for the best available treatments and support

The high and increasing costs of innovative cancer medicines are well recognised [128–131]. Regulatory and reimbursement policies have an important impact on access to these medicines [132–134]. If reimbursement is well aligned with guidelines and optimal clinical practice, healthcare provision is more cost effective and limited resources can be distributed more equitably [3]. This topic was covered extensively in the EBCC-12 manifesto [3] and will not be rediscussed here. However, it is worth highlighting that for many patients with mBC, new and effective drugs may not be available if they are not routinely reimbursed in a country.

A unified regulatory approval process for the European Union means that approval is synchronised within its member countries. Nevertheless, the pace at which medicines reach eligible patients is variable and there are opportunities to improve access [135]. Patients can sometimes access new treatments through early-access programmes or off-label use, but even these show disparities between and within countries [136]. Improving pricing and reimbursement timelines, fostering collaboration between national health authorities and market authorisation holders, and implementing nationally harmonised data-generating early-access programmes can enhance timely and equitable access to innovative cancer treatments [135].

Recommendation 4. Ensure that all patients with mBC in Europe have access to high-quality multidisciplinary information and care (imaging, molecular biology, pathology, radiation, systemic therapy, surgery, side-effect management, palliative and supportive care, physical exercise, trials, etc).

5. Clinical research

5.1. Broaden access and include patient-centred goals in research to improve patient outcomes

Clinical research represents an important means of improving patient outcomes in mBC. Clinical trials offer the opportunity for innovative treatments and improved survival, irrespective of the intervention's efficacy [137–139]. Indeed, simply being treated in a research-active hospital seems to improve outcomes irrespective of whether the individual enrols in a trial. However, access to clinical trials varies according to country, geographical location (urban versus rural), race and other factors [5,11,140–142]. Trials are typically conducted in high-income countries [13,143,144], even though the largest gains in cancer control may be achieved in areas with the poorest cancer outcomes [13]. Some patients cross borders to participate in clinical trials that give access to treatments not available in their home country [144]. Patients

older than 70 years, those of a lower socioeconomic status and minority groups are often under-represented in clinical trials [145–150], and there is typically limited ethnic and racial diversity [143]. This in turn leads to less generalisable results and uncertainty about benefits in minority or under-represented populations [13].

Barriers to clinical trial participation include complex informed consent processes [151], physical distance from participating centres [90], financial barriers such as transport costs, lack of childcare support or time off work or caring duties, language or cultural barriers, lack of trust and misinformation [143]. In addition, patients with brain metastases or those with very aggressive, early relapsing disease are often excluded from clinical trials, even though further research is needed for these patients.

Precision medicine and a deeper understanding of cancer biology has led to increased complexity in clinical trial designs, often involving central assessment of tumour samples with the associated practical and logistical demands, high screen failure rates and recruitment challenges. In addition, EU legal and regulatory requirements, such as for in vitro diagnostic medical devices, can be difficult to meet. Biospecimens donated from patients who participate in clinical trials and their associated biomarker reports should be open access (i.e. available to all researchers in the field), broadening the potential to generate new hypotheses and new clinical trials.

While sophisticated drug development and regulatory clinical trials remain a priority, multidisciplinary, pragmatic and independent clinical trials with practice-changing potential should be facilitated in Europe [13,152]. Trials answering clinically relevant questions about therapeutic strategies based on medically meaningful endpoints should be open to as many patients from as diverse backgrounds as possible. Modifying site management practices and using shorter, more focused case report forms could reverse the spiralling costs of clinical trials without a detrimental impact on quality [153]. Pragmatic trials representative of real-life populations ensure robust methodology for decision making and minimise uncertainty about a drug's effectiveness [151].

In parallel with broadening access to clinical trials, more should be done to improve the way in which research is conducted. Trials should aim higher and be more ambitious, striving to improve the endpoints of greatest importance to patients [152,154]. The Common Sense Oncology movement strives to ensure that cancer care focuses on outcomes that matter to patients [154]. Initiatives of the EU Mission for Cancer aim to increase access to optimised affordable treatment interventions, with a particular focus on simple practical trials in oncology [152]. Unfortunately, some healthcare and funding systems may result in the overuse of treatments that offer very modest improvements in outcomes, while in other systems people cannot access cost-effective treatments that bring substantial and meaningful benefits [154]. To enhance research in underserved populations, where the greatest strides in cancer care may be made, funding from international research initiatives should be more equitable, supporting neglected research priorities and strengthening research capacity and infrastructure in low- and middle-income countries [13].

Academic- and government-led trials that assess less resource-intense schedules or strategies may also alleviate disparity, for example with lower doses, less frequent dosing or shorter treatment durations [155]. Dose optimisation may improve tolerability while maintaining efficacy, but is often overlooked in clinical trials [156,157]. In mBC, efficiency research, exemplified by trials such as SONIA [158], provides an opportunity to limit the impact of expensive drugs on healthcare budgets by using them more efficiently [129]. Furthermore, if cost savings generated from less intensive regimens are reinvested, such trials may be self-funding.

There is currently no mechanism to fund and organise Europe-wide trials answering critical questions in mBC that are outside the regulatory interests of pharmaceutical companies. National organisations exist in some countries, but for specific questions or in rare settings, a coordinated overarching European collaboration would provide answers faster. The HORIZON programme demonstrates that a Europe-wide strategy is feasible [159], but current HORIZON trials do not specifically address mBC. The Cancer Medicines Forum, coordinated by the European Medicines Agency and the European Organisation for the Research and Treatment of Cancer (EORTC), although not breast cancer-specific, is currently the most advanced policy mechanism for treatment optimisation in Europe [160].

Recommendation 5. Ensure there is a mechanism to fund Europe-wide pragmatic optimisation trials to address questions of public interest.

6. Quality indicators to measure access and quality of care

Quality indicators (QIs) are measurable parameters for performance monitoring. Without registries to document predefined guidelines and goals, QIs cannot be monitored or used to implement or adapt policies to ensure equitable access. In 2023, QIs for mBC were published by the European Society of Breast Cancer Specialists (EUSOMA) and the ABC Global Alliance [161]. QIs for evaluating cancer care in low- and middle-income countries have also been developed, understanding that health system infrastructure/availability differs among countries [16]. Therefore, QIs are an important tool to identify inequality.

The task now is to determine adherence to QIs. European accreditation for breast units is voluntary, but most countries have certification bodies and systems to determine quality of care. Some countries, including Germany, Austria and Italy, have mandatory certification systems. QI data can be used as an advocacy tool to mobilise resources and provide accountability and transparency to the public and funders [162].

Adherence to quality assurance protocols for radiation therapy planning has been shown to minimise toxicity and improve survival. A recent consensus document from the European Society for Radiotherapy and Oncology (ESTRO) recommended implementing a culture of quality assurance and treatment recording according to predefined guidelines in both clinical trials and daily practice. The aim is to ensure the generation of high-quality data, especially as novel systemic therapies are constantly being introduced into practice, and their safety in combination with radiation therapy is unknown [163].

Recommendation 6. Ensure the implementation of newly established quality indicators across Europe.

The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) is well established and helps healthcare providers to prioritise finite resources [164]. However, no similar tool is available for non-pharmaceutical interventions. Such a tool would bring value and reduce inequity by avoiding the use of treatments that lack high-level evidence (sometimes the incurable nature of disease leads to more empiric, less evidence-based treatment), and improve accessibility by helping payers prioritise those strategies bringing the greatest clinical benefit, allowing wiser spending and more equitable access. Work is already underway to develop such an instrument to assess value in radiation therapy [165].

Recommendation 7. Consider developing and introducing a tool to rate the importance of interventions beyond anticancer drugs (similar to the ESMO-MCBS for drugs).

7. Conclusion

Several recurring themes emerge when exploring inequalities in access to care for people living with mBC: the elderly, those living in rural areas, those with lower educational or socioeconomic status, certain cultural and racial groups, and those with reduced financial means are more likely to be affected by inequalities and have inferior care, especially in healthcare systems with minimal or no national social support for health, where affordability governs access. This manifesto urges

action to overcome these disparities (Table 1).

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Declaration of Competing Interest

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Table 1
Summary of recommendations.

Theme	Recommendation
Living with the stigma of mBC	Increase the visibility of mBC to society and facilitate the involvement of people with mBC in trials, the workplace and everyday life as much as they want and are able
Registries and real-world data	Implement a national cancer registry recording stage at diagnosis and relapses in every European country and share with the International Agency for Research on Cancer (IARC) to understand how many people are living with mBC
	Harmonise, monitor and use routinely collected real-world and registry data (including but not limited to details of biomarker/genetic testing, treatment and quality of life) to support reimbursement policies and improve access to treatment, trials and services and to evaluate outcomes
Multidisciplinary care	Ensure that all patients with mBC in Europe have access to high-quality multidisciplinary information and care (imaging, molecular biology, pathology, radiation, systemic therapy, surgery, side-effect management, palliative and supportive care, physical exercise, trials, etc.)
Clinical research	Ensure there is a mechanism to fund Europe-wide pragmatic optimisation trials to address questions of public interest
Quality indicators to measure access and quality of care	Ensure the implementation of newly established quality indicators across Europe
	Consider developing and introducing a tool to rate the importance of interventions beyond anticancer drugs (similar to the ESMO-MCBS for drugs)

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References

[1] Ribeiro J, Cardoso MJ. Highlights from the Tenth European Breast Cancer Conference (EBCC10), Amsterdam, 9-11 March 2016. Ecancermedicalscience 2016;10:644.
[2] Cardoso F, Cataliotti L, Costa A, Knox S, Marotti L, Rutgers E, et al. European Breast Cancer Conference manifesto on breast centres/units. Eur J Cancer 2017; 72:244–50.
[3] Cardoso F, MacNeill F, Penault-Llorca F, Eniu A, Sardanelli F, Nordström EB, et al. Why is appropriate healthcare inaccessible for many European breast cancer patients? - The EBCC 12 manifesto. Breast 2021;55:128–35.
[4] Schmidt MK, Kelly JE, Brédart A, Cameron DA, de Boniface J, Easton DF, et al. EBCC-13 manifesto: Balancing pros and cons for contralateral prophylactic mastectomy. Eur J Cancer 2023;181:79–91.
[5] Aldrighetti CM, Niemierko A, Van Allen E, Willers H, Kamran SC. Racial and ethnic disparities among participants in precision oncology clinical studies. JAMA Netw Open 2021;4:e2133205.
[6] Reeder-Hayes K, Roberson ML, Wheeler SB, Abdou Y, Troester MA. From Race to Racism and Disparities to Equity: An Actionable Biopsychosocial Approach to Breast Cancer Outcomes. Cancer J 2023;29:316–22.
[7] Eaker S, Halmin M, Bellocco R, Bergkvist L, Ahlgren J, Holmberg L, et al. Social differences in breast cancer survival in relation to patient management within a National Health Care System (Sweden). Int J Cancer 2009;124:180–7.
[8] Barrios CH. Global challenges in breast cancer detection and treatment. Breast 2022;62:S3–6.
[9] Trapani D, Ginsburg O, Fadelu T, Lin NU, Hassett M, Ilbawi AM, et al. Global challenges and policy solutions in breast cancer control. Cancer Treat Rev 2022; 104.
[10] Grant SJ, Yanguela J, Odebunmi O, Grimshaw AA, Giri S, Wheeler SB. Systematic review of interventions addressing racial and ethnic disparities in cancer care and health outcomes. J Clin Oncol 2024. 0:JCO.23.01290.
[11] Donna E. 2021 survey report: metastatic breast cancer quality of care and quality of life from the patient's perspective in Europe. EUROPA DONNA; 2022.

[12] Bagenal J, McKee M. Brexit and health: 4 years on. Lancet 2024;403:705–7.
[13] Lancet T. Cancer research equity: innovations for the many, not the few. Lancet 2024;403:409.
[14] Wilkerson AD, Gentle CK, Ortega C, Al-Hilli Z. Disparities in breast cancer care-how factors related to prevention, diagnosis, and treatment drive inequity. Healthc (Basel) 2024;12:462.
[15] Batouli A, Jahanshahi P, Gross CP, Makarov DV, Yu JB. The global cancer divide: Relationships between national healthcare resources and cancer outcomes in high-income vs. middle- and low-income countries. J Epidemiol Glob Health 2014;4:115–24.
[16] McLeod M, Torode J, Leung K, Bhoo-Pathy N, Booth C, Chakowa J, et al. Quality indicators for evaluating cancer care in low-income and middle-income country settings: a multinational modified Delphi study. Lancet Oncol 2024;25. e63-e72.
[17] Vancoppenolle J, Franzen N, Koole S, Azarang L, Menezes R, Retel V, et al. Financial Toxicity and Socio-economic Consequences of Cancer Care, A Patient Perspective. Seattle, WA, USA: AcademyHealth Annual Research Meeting,; 2023.
[18] Lengyel CG, Habeeb BS, Altuna SC, Trapani D, Khan SZ, Hussain S. The global landscape on the access to cancer medicines for breast cancer: the ONCOLLEGE experience. Cancer Treat Res 2023;188:353–68.
[19] Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623–49.
[20] Wuerstlein R, Cardoso F, Haidinger R. Expert discussion: Highlights from ABC6: Bridging the gap and insights in this first virtual ABC conference and from 10 years ABC consensus. Breast Care (Basel) 2022;17:107–12.
[21] Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in breast cancer incidence and mortality in Europe – a systematic review and meta-analysis. Eur J Public Health 2016;26:804–13.
[22] Miglietta F, Visani L, Marini S, Griguolo G, Vernaci GM, Bottosso M, et al. Oligometastatic breast cancer: Dissecting the clinical and biological uniqueness of this emerging entity. Can we pursue curability? Cancer Treat Rev 2022;110: 102462.
[23] Grimm M, Radcliff L, Giles M, Nash R, Holley E, Panda S, et al. Living with advanced breast cancer: a descriptive analysis of survivorship strategies. J Clin Med 2022;11:3992.
[24] Vrinten C, Gallagher A, Waller J, Marlow LAV. Cancer stigma and cancer screening attendance: a population based survey in England. BMC Cancer 2019; 19:566.
[25] Akin-Odanye EO, Husman AJ. Impact of stigma and stigma-focused interventions on screening and treatment outcomes in cancer patients. Ecancermedicalscience 2021;15:1308.
[26] Janssen S, Vancoppenolle J, Franzen N, Van Der Graaf WTA, Husson O, Retel VP, et al. Socio-economic consequences among adolescent and young adult cancer patients: A European perspective. Ann Oncol 2023;34(Suppl 2)). S927 (Abstr 1694MO).
[27] Ngan TT, Tien TH, Donnelly M, O'Neill C. Financial toxicity among cancer patients, survivors and their families in the United Kingdom: a scoping review. J Public Health 2023;45:e702–13.
[28] Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). Breast 2018;39:131–8.
[29] Coles CE, Anderson BO, Cameron D, Cardoso F, Horton R, Knaul FM, et al. The Lancet Breast Cancer Commission: tackling a global health, gender, and equity challenge. Lancet 2022;399:1101–3.
[30] DONNA E. Highlights from ED's MBC advocacy webinar June 2023. 2023.
[31] N.Z. BCF. "I'm still here". Insights into living – and dying – with advanced breast cancer in New Zealand. 2018.
[32] Geurts SME, Ibragimova KIE, Ding N, Meegdes M, Erdkamp F, Heijns JB, et al. Time trends in real-world treatment patterns and survival in patients diagnosed with de novo HER2+ metastatic breast cancer: an analysis of the SONABRE registry. Breast Cancer Res Treat 2024.
[33] Gobbini E, Ezzalfani M, Dieras V, Bachelot T, Brain E, Debled M, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer 2018;96:17–24.
[34] DONNA E. The Cancer Currency. 2023.
[35] Alliance A.G. What's it like to live with advanced breast cancer? 2023.
[36] Coles CE, Earl H, Anderson BO, Barrios CH, Bienz M, Bliss JM, et al. The Lancet Breast Cancer Commission. Lancet 2024;403:1895–950.
[37] Commission E. Europe's Beating Cancer Plan. 2023.
[38] Wagstaff A. Does being a patient have to be a full-time job? Cancerworld. 2017.
[39] Kagalwalla S, Tsai AK, George M, Waldock A, Davis S, Jewett P, et al. Consuming patients' days: time spent on ambulatory appointments by people with cancer. Oncologist 2024.
[40] Matos L, Borges M, Oliveira AT, Bulhosa C, Miguel LS, Cunha R, et al. The impact on productivity costs of reducing unemployment in patients with advanced breast cancer: a model estimation based on a Portuguese nationwide observational study. Breast 2023;71. S28 (Abstract OR46).
[41] Nadkarni AR, Vijayakumaran SC, Gupta S, Divatia JV. Mortality in cancer patients with COVID-19 who are admitted to an ICU or who have severe COVID-19: a systematic review and meta-analysis. JCO Glob Oncol 2021;7:1286–305.
[42] Hantel A, Marron JM, Casey M, Kurtz S, Magnavita E, Abel GA. US State government crisis standards of care guidelines: implications for patients with cancer. JAMA Oncol 2021;7:199–205.
[43] Vaz-Luis I, Masiero M, Cavaletti G, Cervantes A, Chlebowski RT, Curigliano G, et al. ESMO Expert Consensus Statements on Cancer Survivorship: promoting high-quality survivorship care and research in Europe. Ann Oncol 2022;33: 1119–33.
[44] Jefford M, Howell D, Li Q, Lisy K, Maher J, Alfano CM, et al. Improved models of care for cancer survivors. Lancet 2022;399:1551–60.
[45] Oostra DL, Burse NR, Wolf LJ, Schleicher E, Mama SK, Bluethmann S, et al. Understanding nutritional problems of metastatic breast cancer patients: opportunities for supportive care through eHealth. Cancer Nurs 2021;44:154–62.
[46] Di Lascio S, Pagani O. Is it time to address survivorship in advanced breast cancer? A review article. Breast 2017;31:167–72.
[47] De Angelis R, Demuru E, Baili P, Troussard X, Katalinic A, Chirlaque Lopez MD, et al. Complete cancer prevalence in Europe in 2020 by disease duration and country (EUROCARE-6): a population-based study. Lancet Oncol 2024;25: 293–307.
[48] In H, Bilimoria KY, Stewart AK, Wroblewski KE, Posner MC, Talamonti MS, et al. Cancer recurrence: an important but missing variable in national cancer registries. Ann Surg Oncol 2014;21:1520–9.
[49] Michalek IM, Martos C, Caetano Dos Santos FL, Giusti F, Degerlund H, Neamtiu L, et al. Advancing data collection and analysis: 2023 revised European network of cancer registries recommendations for standard dataset. Eur J Cancer 2024;199: 113557.
[50] Charalambous A, Price R, Jha P. Accelerating progress on EU cancer control. Lancet Oncol 2024;25:158–60.
[51] McPhail S, Barclay ME, Johnson SA, Swann R, Alvi R, Barisic A, et al. Use of chemotherapy in patients with oesophageal, stomach, colon, rectal, liver, pancreatic, lung, and ovarian cancer: an International Cancer Benchmarking Partnership (ICBP) population-based study. Lancet Oncol 2024;25:338–51.
[52] Topham JT, Lawlor RT, Lemaire D, Casolino R, Biankin AV. Data sharing in cancer research: perceived risks and the consequences of not sharing. Lancet Oncol 2024;25:275–6.
[53] van Maaren MC, Kneepkens RF, Verbaan J, Huijgens PC, Lemmens V, Verhoeven RHA, et al. A conditional model predicting the 10-year annual extra mortality risk compared to the general population: a large population-based study in Dutch breast cancer patients. PLoS One 2019;14. e0210887.
[54] Voets MM, Hassink NS, Veltman J, Slump CH, Koffijberg H, Siesling S. Opportunities for personalised follow-up in breast cancer: the gap between daily practice and recurrence risk. Breast Cancer Res Treat 2024.
[55] Wolfkamp W, Meijer J, van Hoeve JC, van Erning F, de Geus-Oei LF, de Hingh I, et al. Impact of the COVID-19 pandemic on the in-hospital diagnostic pathway of breast and colorectal cancer in the Netherlands: A population-based study. Cancer Med 2024;13. e6861.
[56] de Wild SR, Koppert LB, de Munck L, Vrancken Peeters M, Siesling S, Smidt ML, et al. Prognostic effect of nodal status before and after neoadjuvant chemotherapy in breast cancer: a Dutch population-based study. Breast Cancer Res Treat 2024; 204:277–88.
[57] Otten JDM, Verbeek ALM, Broeders MJM. Long-term cause of death patterns and mode of breast cancer detection in The Netherlands, 2004-2019. J Med Screen 2023;30:217–9.
[58] Meegdes M, Geurts SME, Erdkamp FLG, Dercksen MW, Vriens B, Aaldering KNA, et al. Real-world time trends in overall survival, treatments and patient characteristics in HR+/HER2- metastatic breast cancer: an observational study of the SONABRE Registry. Lancet Reg Health Eur 2023;26:100573.
[59] Ibragimova KIE, Geurts SME, Meegdes M, Erdkamp F, Heijns JB, Tol J, et al. Outcomes for the first four lines of therapy in patients with HER2-positive advanced breast cancer: results from the SONABRE registry. Breast Cancer Res Treat 2023;198:239–51.
[60] Schneider PP, Ramaekers BL, Pouwels X, Geurts S, Ibragimova K, de Boer M, et al. Direct medical costs of advanced breast cancer treatment: a real-world study in the southeast of The Netherlands. Value Health 2021;24:668–75.
[61] Jacquet E, Lardy-Cléaud A, Pistilli B, Franck S, Cottu P, Delaloge S, et al. Endocrine therapy or chemotherapy as first-line therapy in hormone receptor-positive HER2-negative metastatic breast cancer patients. Eur J Cancer 2018;95: 93–101.
[62] Galvin A, Courtinard C, Bouteiller F, Gourgou S, Dalenc F, Jacot W, et al. First-line real-world treatment patterns and survival outcomes in women younger or older than 40 years with metastatic breast cancer in the real-life multicenter French ESME cohort. Eur J Cancer 2024;196:113422.
[63] Le Du F, Carton M, Bachelot T, Saghatchian M, Pistilli B, Brain E, et al. Real-world impact of adjuvant anti-HER2 treatment on characteristics and outcomes of women with HER2-positive metastatic breast cancer in the ESME program. Oncologist 2023;28:e867–76.
[64] Grinda T, Antoine A, Jacot W, Cottu PH, de la Motte Rouge T, Frenel JS, et al. Real-world clinical and survival outcomes of patients with early relapsed triple-negative breast cancer from the ESME national cohort. Eur J Cancer 2023;189: 112935.
[65] Deluche E, Antoine A, Bachelot T, Lardy-Cleaud A, Dieras V, Brain E, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. Eur J Cancer 2020;129:60–70.
[66] Katalinic A, Halber M, Meyer M, Pflüger M, Eberle A, Nennecke A, et al. Population-based clinical cancer registration in Germany. Cancers (Basel) 2023; 15:3934.
[67] Gorasso V, Vandevijvere S, Van der Heyden J, Pelgrims I, Hilderink H, Nusselder W, et al. The incremental healthcare cost associated with cancer in Belgium: A registry-based data analysis. Cancer Med 2024;13. e6659.
[68] de Boniface J, Szulkin R, Johansson ALV. Medical and surgical postoperative complications after breast conservation versus mastectomy in older women with

breast cancer: Swedish population-based register study of 34 139 women. Br J Surg 2023;110:344–52.
[69] Lundberg FE, Kroman N, Lambe M, Andersson TM, Engholm G, Johannesen TB, et al. Age-specific survival trends and life-years lost in women with breast cancer 1990-2016: the NORDCAN survival studies. Acta Oncol 2022;61:1481–9.
[70] Ramsey SD, Onar-Thomas A, Wheeler SB. Real-world database studies in oncology: a call for standards. J Clin Oncol 2024;42:977–80.
[71] Cottu P, Ramsey SD, Solà-Morales O, Spears PA, Taylor L. The emerging role of real-world data in advanced breast cancer therapy: Recommendations for collaborative decision-making. Breast 2022;61:118–22.
[72] ESMO. ESMO real world data and digital health working group. 2024.
[73] EMA. Data analysis and real world interrogation network (DARWIN EU®) 2024.
[74] Commission E. Implementation of the regulation on health technology assessment. 2024.
[75] Haier J, Schaefers J. Economic perspective of cancer care and its consequences for vulnerable groups. Cancers 2022;14:3158.
[76] Guillaume E, Rollet Q, Launay L, Beuriot S, Dejardin O, Notari A, et al. Evaluation of a mobile mammography unit: concepts and randomized cluster trial protocol of a population health intervention research to reduce breast cancer screening inequalities. Trials 2022;23:562.
[77] Tabár L, Chen TH, Yen AM, Dean PB, Smith RA, Jonsson H, et al. Early detection of breast cancer rectifies inequality of breast cancer outcomes. J Med Screen 2021;28:34–8.
[78] Hölzel D, Eckel R, Bauerfeid I, Baier B, Beck T, Braun M, et al. Survival of de novo stage IV breast cancer patients over three decades. J Cancer Res Clin Oncol 2017; 143:509–19.
[79] Benitez Fuentes JD, Morgan E, de Luna Aguilar A, Mafra A, Shah R, Giusti F, et al. Global stage distribution of breast cancer at diagnosis: a systematic review and meta-analysis. JAMA Oncol 2024;10:71–8.
[80] Nguyen-Pham S, Leung J, McLaughlin D. Disparities in breast cancer stage at diagnosis in urban and rural adult women: a systematic review and meta-analysis. Ann Epidemiol 2014;24:228–35.
[81] Williams F, Jeanetta S, James AS. Geographical location and stage of breast cancer diagnosis: a systematic review of the literature. J Health Care Poor Under 2016;27:1357–83.
[82] Delacôte C, Ariza JM, Delacour-Billon S, Ayrault-Piault S, Borghi G, Menanteau K, et al. Socioeconomic and geographic disparities of breast cancer incidence according to stage at diagnosis in France. Cancer Causes Control 2024;35:241–51.
[83] Kesson EM, Allardice GM, George WD, Burns HJG, Morrison DS. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. Br Med J 2012;344: e2718.
[84] Pangarsa EA, Rizky D, Tandarto K, Setiawan B, Santosa D, Hadiyanto JN, et al. The effect of multidisciplinary team on survival rates of women with breast cancer: a systematic review and meta-analysis. Ann Med Surg (Lond) 2023;85: 2940–8.
[85] Magnoni F, Tinterri C, Corso G, Curigliano G, Leonardi MC, Toesca A, et al. The multicenter experience in the multidisciplinary Italian breast units: a review and update. Eur J Cancer Prev 2023.
[86] Taylor C, Harris J, Stenner K, Sevdalis N, Green SAJ. A multi-method evaluation of the implementation of a cancer teamwork assessment and feedback improvement programme (MDT-FIT) across a large integrated cancer system. Cancer Med 2021;10:1240–52.
[87] Morgan JL, Cheng V, Barry PA, Copson E, Cutress RI, Dave R, et al. The MARECA (national study of management of breast cancer locoregional recurrence and oncological outcomes) study: National practice questionnaire of United Kingdom multi-disciplinary decision making. Eur J Surg Oncol 2022;48:1510–9.
[88] Ignatiadis M, Sledge GW, Jeffrey SS. Liquid biopsy enters the clinic - implementation issues and future challenges. Nat Rev Clin Oncol 2021;18: 297–312.
[89] Horgan D, Ciliberto G, Conte P, Curigliano G, Seijo L, Montuenga LM, et al. Bringing onco-innovation to Europe's healthcare systems: the potential of biomarker testing, real world evidence, tumour agnostic therapies to empower personalised medicine. Cancers (Basel) 2021;13:583.
[90] Crimini E, Tini G, Tarantino P, Ascione L, Repetto M, Beria P, et al. Evaluation of the geographical accessibility of genome-matched clinical trials on a national experience. Oncologist 2024;29:159–65.
[91] Simons M, Uyl-de Groot CA, Retèl VP, Mankor JM, Ramaekers BLT, Joore MA, et al. Cost-effectiveness and budget impact of future developments with whole-genome sequencing for patients with lung cancer. Value Health 2023;26:71–80.
[92] Miglietta F, Bottosso M, Griguolo G, Dieci MV, Guarneri V. Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival. ESMO Open 2022;7:100409.
[93] Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32:1475–95.
[94] Normanno N, Apostolidis K, Wolf A, Al Dieri R, Deans Z, Fairley J, et al. Access and quality of biomarker testing for precision oncology in Europe. Eur J Cancer 2022;176:70–7.
[95] Bogavac-Stanojevic N, Jelic-Ivanovic Z. The cost-effective laboratory: implementation of economic evaluation of laboratory testing. J Med Biochem 2017;36:238–42.
[96] deSouza NM, Liu Y, Chiti A, Oprea-Lager D, Gebhart G, Van Beers BE, et al. Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer 2018;91:153–63.
[97] Pasquier, Bidaut D, Oprea-Lager DE L, deSouza NM, Krug D, Collette L, et al. Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups. Lancet Oncol 2023;24. e331-e43.
[98] Viale G, Mastropasqua MG. What can the pathologist offer for optimal treatment choice? Ann Oncol 2010;21(Suppl 7). vii27-9.
[99] Grinda T, Joyon N, Lusque A, Lefèvre S, Arnould L, Penault-Llorca F, et al. Phenotypic discordance between primary and metastatic breast cancer in the large-scale real-life multicenter French ESME cohort. NPJ Breast Cancer 2021;7: 41.
[100] Gogia A, Deo SVS, Sharma D, Phulia RK, Thulkar S, Malik PS, et al. Discordance in biomarker expression in breast cancer after metastasis: single center experience in India. J Glob Oncol 2019;(5):1–8.
[101] Le Tourneau C, Delord J-P, Gonçalves A, Gavoille C, Dubot C, Isambert N, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 2015;16: 1324–34.
[102] Simmons C, Miller N, Geddie W, Gianfelice D, Oldfield M, Dranitsaris G, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol 2009;20:1499–504.
[103] Amir E, Miller N, Geddie W, Freedman O, Kassam F, Simmons C, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol 2012;30:587–92.
[104] Aurilio G, Monfardini L, Rizzo S, Sciandivasci A, Preda L, Bagnardi V, et al. Discordant hormone receptor and human epidermal growth factor receptor 2 status in bone metastases compared to primary breast cancer. Acta Oncol 2013; 52:1649–56.
[105] Aftimos P, Oliveira M, Irrthum A, Fumagalli D, Sotiriou C, Gal-Yam EN, et al. Genomic and transcriptomic analyses of breast cancer primaries and matched metastases in AURORA, the Breast International Group (BIG) molecular screening initiative. Cancer Discov 2021;11:2796–811.
[106] Henry NL, Somerfield MR, Dayao Z, Elias A, Kalinsky K, McShane LM, et al. Biomarkers for systemic therapy in metastatic breast cancer: ASCO guideline update. J Clin Oncol 2022;40:3205–21.
[107] Andre F, Filleron T, Kamal M, Mosele F, Arnedos M, Dalenc F, et al. Genomics to select treatment for patients with metastatic breast cancer. Nature 2022;610: 343–8.
[108] Zahnd WE, Ranganathan R, Adams SA, Babatunde OA. Sociodemographic disparities in molecular testing for breast cancer. Cancer Causes Control 2022;33: 843–59.
[109] Baars JE, van Dulmen AM, Velthuizen ME, Theunissen EB, Vrouenraets BC, Kimmings AN, et al. Migrant breast cancer patients and their participation in genetic counseling: results from a registry-based study. Fam Cancer 2016;15: 163–71.
[110] van de Ven M, Simons M, Koffijberg H, Joore MA, MJ IJ, Retèl VP, et al. Whole genome sequencing in oncology: using scenario drafting to explore future developments. BMC Cancer 2021;21:488.
[111] Bayle A, Bonastre J, Chaltiel D, Latino N, Rouleau E, Peters S, et al. ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. Ann Oncol 2023;34:934–45.
[112] Torr B, Jones C, Choi S, Allen S, Kavanaugh G, Hamill M, et al. A digital pathway for genetic testing in UK NHS patients with cancer: BRCA-DIRECT randomised study internal pilot. J Med Genet 2022;59:1179–88.
[113] Ryska A, Berzinec P, Brcic L, Cufer T, Dziadziuszko R, Gottfried M, et al. NSCLC molecular testing in Central and Eastern European countries. BMC Cancer 2018; 18:269.
[114] André F, Rassy E, Marabelle A, Michiels S, Besse B. Forget lung, breast or prostate cancer: why tumour naming needs to change. Nature 2024;626:26–9.
[115] Pascual J, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol 2022;33:750–68.
[116] Febbo PG, Allo M, Alme EB, Carter GC, Dumanois R, Essig A, et al. Recommendations for the equitable and widespread implementation of liquid biopsy for cancer care. JCO Precis Oncol 2024;(8):e2300382.
[117] Gannon MR, Dodwell D, Aggarwal A, Park MH, Miller K, Horgan K, et al. Evidence into practice: a national cohort study of NICE-recommended oncological drug therapy utilisation among women diagnosed with invasive breast cancer in England. Br J Cancer 2023;129:1569–79.
[118] Nguyen EK, Ruschin M, Zhang B, Soliman H, Myrehaug S, Detsky J, et al. Stereotactic body radiotherapy for spine metastases: a review of 24 Gy in 2 daily fractions. J Neurooncol 2023;163:15–27.
[119] van der Linden YM, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CA, et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. Int J Radiat Oncol Biol Phys 2004;59:528–37.
[120] Guckenberger M, Andratschke N, Belka C, Bellut D, Cuccia F, Dahele M, et al. ESTRO clinical practice guideline: Stereotactic body radiotherapy for spine metastases. Radio Oncol 2023;190:109966.
[121] Haun MW, Estel S, Rücker G, Friederich HC, Villalobos M, Thomas M, et al. Early palliative care for adults with advanced cancer. Cochrane Database Syst Rev 2017;6. Cd011129.
[122] Chelazzi C, Ripamonti CI. How early should be "early integrated palliative care"? Support Care Cancer 2023;32:41.

[123] Fairchild A, Hill J, Alhumaid M, Rau A, Ghosh S, Le A, et al. Palliative radiotherapy delivery by a dedicated multidisciplinary team facilitates early integration of palliative care: A secondary analysis of routinely collected health data. J Med Imaging Radiat Sci 2022;53:S51–5.
[124] Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet 2014;383:1721–30.
[125] May A.H.A., Depenbusch J. Effects of a structured and individualized exercise program on fatigue and health-related quality of life in patients with metastatic breast cancer: The multinational randomized controlled PREFERABLE-EFFECT study.Abstract GS02–10.
[126] Hearn J, Higginson IJ. Do specialist palliative care teams improve outcomes for cancer patients? A systematic literature review. Palliat Med 1998;12:317–32.
[127] Frasca M, Sabathe C, Delaloge S, Galvin A, Patsouris A, Levy C, et al. Palliative care delivery according to age in 12,000 women with metastatic breast cancer: Analysis in the multicentre ESME-MBC cohort 2008-2016. Eur J Cancer 2020; 137:240–9.
[128] Franzen N, Romagnoli G, Ziegler A, Retèl VP, Offerman TJS, van Harten WH. Improving the affordability of anticancer medicines demands evidence-based policy solutions. Cancer Discov 2022;12:299–302.
[129] van Ommen-Nijhof A, Retèl VP, van den Heuvel M, Jager A, van Harten WH, Sonke GS. A revolving research fund to study efficient use of expensive drugs: big wheels keep on turning. Ann Oncol 2021;32:1212–5.
[130] Hofmarcher T, Lindgren P, Wilking N, Jönsson B. The cost of cancer in Europe 2018. Eur J Cancer 2020;129:41–9.
[131] Vivot A, Jacot J, Zeitoun JD, Ravaud P, Crequit P, Porcher R. Clinical benefit, price and approval characteristics of FDA-approved new drugs for treating advanced solid cancer, 2000-2015. Ann Oncol 2017;28:1111–6.
[132] Ehsan AN, Wu CA, Minasian A, Singh T, Bass M, Pace L, et al. Financial toxicity among patients with breast cancer worldwide: a systematic review and meta-analysis. JAMA Netw Open 2023;6. e2255388-e.
[133] Piccart M, Vansteenkiste J, Prenen H. Rethinking the reimbursement of innovative medicines in oncology: Looking beyond overall survival. Belg J Med Oncol 2023;17:211–5.
[134] Koleva-Kolarova R, Buchanan J, Vellekoop H, Huygens S, Versteegh M. Mölken MR-v, et al. Financing and reimbursement models for personalised medicine: a systematic review to identify current models and future options. Appl Health Econ Health Policy 2022;20:501–24.
[135] Luyendijk M, Blommestein H, Uyl-de Groot C, Siesling S, Jager A. Regulatory approval, reimbursement, and clinical use of cyclin-dependent kinase 4/6 inhibitors in metastatic breast cancer in the Netherlands. JAMA Netw Open 2023; 6:e2256170.
[136] Vancoppenolle JM, Franzen N, Koole SN, Retèl VP, van Harten WH. Differences in time to patient access to innovative cancer medicines in six European countries. Int J Cancer 2024;154:886–94.
[137] Nijjar SK, D'Amico MI, Wimalaweera NA, Cooper N, Zamora J, Khan KS. Participation in clinical trials improves outcomes in women's health: a systematic review and meta-analysis. BJOG 2017;124:863–71.
[138] Jonker L, Fisher SJ. The correlation between National Health Service trusts' clinical trial activity and both mortality rates and care quality commission ratings: a retrospective cross-sectional study. Public Health 2018;157:1–6.
[139] Boaz A, Hanney S, Jones T, Soper B. Does the engagement of clinicians and organisations in research improve healthcare performance: a three-stage review. BMJ Open 2015;5. e009415.
[140] Charton E, Baldini C, Fayet Y, Schultz E, Auroy L, Vallier E, et al. Inequality factors in access to early-phase clinical trials in oncology in France: results of the EGALICAN-2 study. ESMO Open 2023;8:101610.
[141] Mc Grath-Lone L, Day S, Schoenborn C, Ward H. Exploring research participation among cancer patients: analysis of a national survey and an in-depth interview study. BMC Cancer 2015;15:618.
[142] Stout N.L., Nikcevich D., Henderson T.O., Steen P., Weiss M., Ades S., et al. Improving rural clinical trial enrollment: recommendations from the rural health working group of the Alliance Clinical Trials Network. J Clin Oncol.0: JCO.23.01667.
[143] Wilcox. The Health Policy Partnership. Inclusion by design: building equity in clinical trials through the lens of metastatic breast cancer. 2023.
[144] Lalova T, Padeanu C, Negrouk A, Lacombe D, Geissler J, Klingmann I, et al. Cross-border access to clinical trials in the EU: exploratory study on needs and reality. Front Med (Lausanne) 2020;7:585722.
[145] Candelario NM, Major J, Dreyfus B, Sattler D, Paulucci D, Misra S, et al. Diversity in clinical trials in Europe and the USA: a review of a pharmaceutical company's data collection, reporting, and interpretation of race and ethnicity. Ann Oncol 2023;34:1194–7.
[146] Grette KV, White AL, Awad EK, Scalici JM, Young-Pierce J, Rocconi RP, et al. Not immune to inequity: minority under-representation in immunotherapy trials for breast and gynecologic cancers. Int J Gynecol Cancer 2021;31:1403–7.
[147] Parks RM, Holmes HM, Cheung KL. Current challenges faced by cancer clinical trials in addressing the problem of under-representation of older adults: a narrative review. Oncol Ther 2021;9:55–67.
[148] Gopishetty S, Kota V, Guddati AK. Age and race distribution in patients in phase III oncology clinical trials. Am J Transl Res 2020;12:5977–83.
[149] Ramamoorthy A, Knepper TC, Merenda C, Mendoza M, McLeod HL, Bull J, et al. Demographic composition of select oncologic new molecular entities approved by the FDA between 2008 and 2017. Clin Pharm Ther 2018;104:940–8.
[150] Sharrocks K, Spicer J, Camidge DR, Papa S. The impact of socioeconomic status on access to cancer clinical trials. Br J Cancer 2014;111:1684–7.
[151] Ford I, Norrie J. Pragmatic trials. N Engl J Med 2016;375:454–63.
[152] Leary A, Besse B, André F. The need for pragmatic, affordable, and practice-changing real-life clinical trials in oncology. Lancet 2024;403:406–8.
[153] Rawlins MD, Chalkidou K. The opportunity cost of cancer care: a statement from NICE. Lancet Oncol 2011;12:931–2.
[154] Booth CM, Sengar M, Goodman A, Wilson B, Aggarwal A, Berry S, et al. Common Sense Oncology: outcomes that matter. Lancet Oncol 2023;24:833–5.
[155] Mitchell AP, Goldstein DA. Cost savings and increased access with ultra-low-dose immunotherapy. J Clin Oncol 2023;41:170–2.
[156] Zirkelbach JF, Shah M, Vallejo J, Cheng J, Ayyoub A, Liu J, et al. Improving dose-optimization processes used in oncology drug development to minimize toxicity and maximize benefit to patients. J Clin Oncol 2022;40:3489–500.
[157] Moutinho S. Dozens of precision cancer drugs tested at lower doses to reduce side effects and cut costs. Nat Med 2024;30:611–4.
[158] Sonke GS, Nijhof AVO-, Wortelboer N, Noort Vvd, Swinkels ACP, Blommestein HM, et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC). J Clin Oncol 2023. 41: LBA1000-LBA.
[159] EUROPADONNA. Research and clinical trials, 2024.
[160] Agency E.M. EMA establishes Cancer Medicines Forum with academia to optimise cancer treatments in clinical practice, 2022.
[161] Cardoso F, McCartney A, Ponti A, Marotti L, Vrieling C, Eniu A, et al. European Society of Breast Cancer Specialists/Advanced Breast Cancer Global Alliance quality indicators for metastatic breast cancer care. Eur J Cancer 2023;187: 105–13.
[162] WHO. Assessing the development of palliative care worldwide: a set of actionable indicators, 2021.
[163] Kaidar-Person O, Meattini I, Boersma LJ, Becherini C, Cortes J, Curigliano G, et al. Essential requirements for reporting radiation therapy in breast cancer clinical trials: an international multi-disciplinary consensus endorsed by the European SocieTy for Radiotherapy and Oncology (ESTRO). Radio Oncol 2023:110060.
[164] Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017;28: 2340–66.
[165] Sapir E, Cherny NI, Ennis RD, Smith BD, Smith GL, Marks LB, et al. Evaluation of the ESMO-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for adjuvant radiotherapy in breast cancer. ESMO Open 2023;8:101206.