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Socioeconomic Impact of OncotypeDX on Breast Cancer Treatment: Preliminary Results

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Abstract. *Background/Aim: Breast cancer (BC) is the most prevalent oncological diagnosis worldwide. Molecular subtyping has provided valuable insights for treatment decisions, but challenges remain in adjuvant treatment for hormone receptor (HR)-positive/HER2-negative luminal BC (LBC). Multigene markers like Oncotype DX have emerged to provide more precise prognostic information. This study aimed to evaluate the influence of gene expression panels on fear of cancer recurrence (FCR), quality of life (QoL), and healthcare-related greenhouse emissions. Patients and Methods: A monocentric retrospective analysis was conducted using a prospective database of patients undergoing Oncotype DX. QoL assessments were performed using the Short Breast Health Perception Questionnaire (BHPQ) and Life Satisfaction Questionnaire (LSQ-32). Reductions in hospital visits and travel distance were analyzed. Results: Twenty-eight patients underwent Oncotype DX testing. Of these, 17.85% received adjuvant chemotherapy based on the recurrence score (RS). The implementation of Oncotype DX resulted in a significant reduction in hospital visits, travel distance, and healthcare-related greenhouse gas emissions. QoL assessments using BHPQ and LSQ-32 showed lower levels of FCR and improved QoL in various domains for patients who received hormone therapy (HT) alone. Conclusion: The implementation of Oncotype DX in clinical practice has the potential to reduce overtreatment, decrease healthcare-related greenhouse gas emissions, and improve QoL. Lower levels of FCR and improved QoL were observed in patients who received HT-only based on the RS score.*

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Breast cancer (BC) remains the most prevalent oncological diagnosis worldwide, with an annual incidence exceeding 2.3 million cases (1). During the past century, the approach to BC treatment has evolved from a singular surgical procedure to a multidisciplinary treatment strategy that takes into account both tumor and patient-related characteristics, including comorbidities and preferences (2-4).

In the past decade, the classification of BC molecular subtypes has emerged as a significant breakthrough in tumor assessment and management, providing clinicians with a valuable tool to shift adjuvant treatment decisions from relying solely on statistical risk to incorporating predictive biomarker assessment (5). BC distant disease spread is the result of a not fully understood complex interplay between biological processes, including tumor circulation, proliferation, angiogenesis, and the microenvironment of the target tissue (6-8). Although progress has been made, many questions remain unsolved in this area (9-11).

The issue of adjuvant treatment in hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative, luminal BC (LBC) continues to pose challenges. This subtype accounts for nearly 70% of all BC cases (12), and current guidelines recommend adjuvant chemotherapy for patients with more than 3 metastatic lymph nodes (LNs) following upfront surgery in addition to endocrine therapy (ET). Adjuvant treatment is also suggested for patients with up to 3 metastatic lymph nodes (LNs) or tumors larger than 5

Table I. *English translation of Short Breast Health Perception Questionnaire (BHPQ) (23). All questions were answered on a Likert scale: Always=1 point; Very often=2 points; Sometimes=3 points; Rarely=4 points; Never=5 points.*

Short Breast Health Perception Questionnaire (BHPQ)
1 I feel I have a dangerous disease in my breast
2 I feel I will get a dangerous disease in my breast in the future
3 I feel that I am causing trouble for my family due to my breast conditions
4 I feel I have a disorder in my breast that will cause troubles for my family in the future
5 I feel I have a problem in my breasts and this thought makes me anxious
6 I feel I have a problem in my breasts and this thought has disturbed my daily life
7 I feel I have a problem in my breasts and this thought disrupts my sexual activities
8 I need to obsessively examine my breasts to stay calm
9 I need to go for breast checkups sooner than my doctor has recommended for my peace of mind
10 I constantly search for and inquire about new methods for detection of breast disorders
11 I am constantly on the search for new information about breast diseases

cm, taking into consideration other prognostic and predictive factors such as age, histology, HR expression, proliferative index (Ki67), histological grade, and lymph vascular invasion (13). However, despite these indications, chemotherapy administration is still recommended for many patients inspite of the limited benefits, leading to overtreatment in a significant number of women (14, 15).

To address this issue, several multigene markers have been developed to provide more precise prognostic information and predict the potential benefits of adjuvant treatments beyond classical clinical-pathological features alone. One such marker, Oncotype DX (Exact Sciences, Madison, WI, USA), is a gene expression panel consisting of 21 genes (16 tumor-associated and 5 reference genes) (16). Normalized Oncotype DX gene expression analysis determines a recurrence score (RS) from 0 to 100 with higher score associated with higher risk of recurrence (17). Traditional categories were set as follows: low-risk (RS <18), intermediate risk (RS 18-30) and high-risk (RS >30) of recurrence (18). This assay has recently been introduced in the Italian National Health Service for localized LBC subset of patients, with the aim of reducing the risk of overtreatment. While de-escalating treatment has shown promise in improving Patients Reported Outcome Measures (PROM), the impact of Oncotype DX on the cost-effectiveness of treatment and the fear of cancer recurrence (FCR) has only been partially evaluated (19-21). Furthermore, the effect of gene expression panels on healthcare-related greenhouse emissions has not yet been assessed. Therefore, the objective of this current analysis was to evaluate the influence of gene expression panels on FCR, QoL, and the reduction of healthcare-related greenhouse emissions.

Patients and Methods

Study design. A retrospective analysis from our prospective updated database was designed to assess the impact of multigene analysis introduction in our clinical practice. Policlinico Tor Vergata Ethical Committee waived the need of informed consent due to the monocentric design and the lack of clinical intervention in our analysis. Prior to their first visit, all our patients routinely sign an informed consent for clinical practice data analysis. Assessment of the patients' quality of life (QoL) was set as the primary outcome of the study using the Short Breast Health Perception Questionnaire (BHPQ) and Life Satisfaction Questionnaire (LSQ-32) (22, 23). Both questionaries are validated in BC patients and are used to assess patients' QoL related to the treatment. Secondary outcomes were the evaluation of reduction in both the number of visits to hospital and the distance travelled to reach the hospital. Enrollment periods were set from June 2022 and December 2023, representing the first six months of implementation of the Oncotype DX reimbursement policy in our Institution.

Population and study protocol. Primary inclusion criteria were all patients admitted to the Policlinico Tor Vergata outpatient Breast Center facilities during the study period eligible for Oncotype DX (Exact Sciences) after surgery. According to the Lazio Regional Guideline, Oncotype DX testing proposed to every patient with early LBC (stage I-IIIA) according to AJCC 2018 (Edition VIII) recommendations according to TMN classification (24) when clinical-pathological information was not conclusive to recommend adjuvant chemotherapy (25). Once Oncotype DX was proposed by the multidisciplinary tumor board, patients signed informed consent to undergo chemotherapy if RS showed clear adjuvant treatment benefits according to the Lazio Oncotype DX reimbursement guidelines (26, 27).

Exclusion criteria were patients' refusal to undergo Oncotype DX or subsequent chemotherapy administration, or patients who were currently in follow-up in other facilities. After the Oncotype DX test, all patients underwent multidisciplinary visit at which they were informed of the test results and the adjuvant treatment proposed. Data regarding adjuvant treatment were included in the analysis. If patients underwent HT-only, blinded re-evaluation without Oncotype RS score was obtained from a clinical oncologist (IP) with more than 15 years of experience in BC care to determine which adjuvant chemotherapy would have been suggested in HT-only patients if a high RS score had been obtained.

At three months from results communication, assessment of patients' QoL was performed with telephonic follow up during which BHPQ and LSQ-32 were administered (Table I and Table II, respectively). Both questionaries were reported on a Likert scale

Table II. *English translation of Life Satisfaction Questionnaire (LSQ-32) (22). All questions were answered on a Likert scale: Not at all agree=1; Disagree=2; Neither agree nor disagree=3; Somewhat agree=4; Absolutely agree=5.*

Life Satisfaction Questionnaire (LSQ-32)
1 I feel very often tired
2 I feel very often unfit
3 I often have difficulty sleeping
4 I often have a lack of appetite
5 I have frequent episodes of diarrhea
6 I have frequent episodes of constipation
7 I have frequent episodes of dizziness
8 I often have episodes of palpitations
9 I often have difficulty breathing
10 I often have muscle weakness
11 I often have pain
12 I often feel nauseous
13 I am very satisfied with my quality of life
14 I am very satisfied with my domestic situation
15 I am very satisfied with my economic condition
16 I do physical activity daily
17 I feel satisfied with the activities I do
18 I find the activities I do every day very interesting
19 I find very useful the activities that I do every day
20 I find the activities you do every day necessary
21 I find the family relationships I have very satisfying.
22 My family relationships vary constantly
23 I find my family relationships very enjoyable
24 I find my family relationships very important
25 I find my family relationships very independent of my life
26 I find my family relationships very pleasant
27 I find my friendships very satisfying
28 My friendships vary constantly
29 I find my friendships very important
30 I find my friendships very independent of my life
31 I find my friendships very pleasant
32 In general, I feel satisfied with my quality of life

Table III. *Demographic and clinical characteristics of the study group.*

	Study group (n=28)
Age (years)	70.59 (35.5-71.94)
Menopause	
Yes	11 (75.00%)
No	7 (25.00%)
Histology (n)	
IDC	23 (82.14%)
ILC	1 (3.57%)
Other	4 (14.28%)
Grading (n)	
G1	4 (14.28%)
G2	19 (67.85%)
G3	5 (17.86%)
HR expression (mean %) (range)	
ER	70.44% (67.50-95.00)
PR	60.38% (8.75-95.00)
Proliferating factor (ki67%)	21% (18-25)
HER2 Score n (%)	
0	13 (46.43%)
1	13 (46.43%)
2	2 (7.14%)
3	0 (0%)
DCIS n (%)	
Yes (%)	15 (53.57%)
No (%)	13 (46.42%)
Adjuvant treatment n (%)	
Chemotherapy group	5 (17.85%)
HT-only group	23 (82.15%)
Oncotype RS score (0-100) (n)	15.47 (11.00-21.50)
Distance from the hospital (km)	56.34 (34.50-58.50)

All continuous variables are reported as mean and interquartile range. All categorical data were recoded as numbers and percentages. IDC: Invasive ductal carcinoma; ILC: invasive luminal Carcinoma; HR: hormonal receptor; HER2: human epidermal grow factor receptor-2; DCIS ductal carcinoma *in situ*; HT: hormonal treatment; RS: Recurrence score; ER: estrogen receptor; PR: progesterone receptor.

(Always=1 point; Very often=2 points; Sometimes=3 points; Rarely=4 points; Never=5 points). Sub analysis was performed between patients according to the treatment schedule (Chemotherapy group vs. HT-only group).

Data collection and statistical analysis. Retrospective data were collected from a prospectively updated database containing all clinical data including age, personal history, multidisciplinary treatment, and clinicopathological BC variables. Data from pathological examinations such as HR and Ki67 expression are presented as percentage of positive cells in specimens examined using immunohistochemistry. Over-expression of the HER2 gene (HER2 SCORE) was determined using IHC or fluorescence in situ hybridization (FISH), as indicated by the recommendations of the 2018 ASCO/CAP. For continuous variables, means and interquartile range (IQR) were calculated. Statistical analysis was performed using the SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

From June 2022 to December 2022, Oncotype DX testing was proposed to a total of 32 patients at our facility that were considered eligible for enrollment. However, four patients were excluded from the analysis: three patients decided to undergo follow up at other clinical centers and one patient refused to undergo adjuvant treatment if suggested by Oncotype DX. Therefore, a total of 28 consecutive cases were included in the final analysis. Table III summarizes demographic and clinical variables. Median population age was 70.59 and 7 (25.00%) of patients were classified as premenopausal women. Mean Oncotype DX RS was 15.47, and in 5 cases (17.85%) adjuvant treatment with chemotherapy was administered due to the RS score. Mean distance travelled to reach the hospital was calculated as

56.34 km in the study group. After obtaining the RS scores, a total of 340 outpatient visits were not performed for chemotherapy administration in women in the HT-only group. This reduced the distance travelled to reach the hospital by 20,694.58 km resulting in a significant reduction in green-house gas emission.

Regarding patients' QoL, the results from BHPQ and LSQ-32 are summarized in Table IV for the HT-only group. Interestingly, while BHPQ reported intermediate values for questions regarding domains as sexuality, or daily activity, lower values were reported in domains regarding BC awareness and anxiety. Moreover, while LSQ-32 reported higher value in physical symptoms (1-4), lower values were reported in domains assessing sickness impact, quality of everyday activities, socio-economic situation, quality of family relations, and quality of close friend relationship, demonstrating how chemotherapy sparing was associated with less side effects without affecting social and economic domains.

Discussion

BC multigene assay brought a revolution in adjuvant BC care, shifting from a classical clinical-pathological risk assessment to a more in-depth intrinsic tumor biology evaluation, reducing the rate of overtreatment in early LBC patients (16, 28). However, while the beneficial role of BC multigene assay on overtreatment risk has been clearly demonstrated in TAILORx and RxPONDER trials (26, 27), in the present study we examined how Oncotype DX implementation in clinical care may result in potential savings for the national health system, reducing the environmental impact of BC without affecting BC patients' QoL and FCR.

FCR is defined as "fear, worry or concern relating to the possibility that cancer will come back or progress" (29) and represents one of the most unmet psychological needs in BC survivors (30). In fact, while the multidisciplinary approach resulted in a steady reduction in mortality among patients with BC in the last 30 years (31), up to 50% of BC survivors experience during their lifetime moderate to severe FCR, with higher rate among younger women (32, 33). Higher levels of FCR are correlated with decreased QoL and increased levels of anxiety, depression, and psychological distress (34).

FCR often emerges during the vulnerable period after completion of primary treatment and before adjuvant treatment administration (34-36). In this fragile period, communication of the results of multigene assessment such as Oncotype DX may represent a further stressor for patients with BC. Gormley *et al*. demonstrated that higher Oncotype DX RS score may have an impact on FCR and anxiety, our results demonstrated a lower level of FCR in the HT-only group evaluated with BHPQ and LSQ-32 (20). BHPQ represents a valid instrument designed to evaluate breast health perception in BC survivors, exploring different domains related to the effect of BC recurrence on health perception (23). Additionally, the LSQ-32 test was administered to our patients to explore six different domains such as 1) 'Quality of family relation', 2) 'Physical symptoms', 3) 'Socioeconomic situation', 4) 'Quality of daily activities', 5) 'Sickness impact' and 6) 'Quality of close friend relation' (22).

Additionally, de-escalating adjuvant chemotherapy may represent a benefit in terms of health care costs, social costs, and healthcare related green-house gas emission. In fact, in our preliminary analysis, only 5 (17.85%) patients required adjuvant chemotherapy, determining a net reduction of 340 outpatient visits, and 20,694.58 km of distance travelled. Our results confirm the cost-consequence model designed by de Jongh *et al*. to determine the economic impact of different gene expression tests in node negative early breast cancer (EBC). The cost-consequence model, including chemotherapy, short- and long-term event costs, productivity loss, genomic profiling testing costs, cost of cancer recurrence, and hospitalization costs, demonstrated that Oncotype DX may result in an average saving of €6,768 (37). This result is mostly achieved by reducing adverse events, sick days, outpatient visits and hospitalization required in patients undergoing HT.

Additionally, the distance travelled by patients was reduced. In fact, green-house gas emission and climate change have a direct impact on global health care and health policy worldwide because they shift health care resources toward extreme weather events, emerging zoonotic infection, and increasing exposure to air pollutant carcinogenic agents (38-40). Amid the COVID-19 pandemic, Health care providers understood that marginal interventions, such as the incorporation of telemedicine, had the potential to raise healthcare accessibility and concurrently mitigate atmospheric pollutants (41-44). Under this perspective, enhanced sustainability of BC care, the most diagnosed neoplasm worldwide, may eventually contribute to a reduction in the detrimental effects of climate change on global health.

We are aware that our preliminary study has some limitations. First, monocentric and retrospective analysis may have introduced biases. Moreover, the lack of comparative group cannot allow the determination of the effect of multigene assay on QoL of patients. In order to overcome these biases, further multicentric studies comparing patients undergoing Oncotype DX and historical series is currently under development to understand the role of multigene assay on patients' QoL, risk recurrence, health care sustainability, and breast care environment impact.

Despite these limitations, if confirmed in further studies, our study demonstrated that Oncotype DX is an invaluable tool for determining adjuvant treatment in HR positive BC patients without affecting QoL, anxiety, and FCR, while reducing the need for outpatient visits, and thus the carbon footprint of BC care.

Table IV. *Short Breast Health Perception Questionnaire (BHPQ) and Life Satisfaction Questionnaire (LSQ-32) results in the HR-only group.*

	HR-only group (n=28)
BHPQ	
1 I feel I have a dangerous disease in my breast	3.23 (2-5)
2 I feel I will get a dangerous disease in my breast in the future	3.38 (2-5)
3 I feel that I am causing trouble for my family due to my breast conditions	2.92 (1-5)
4 I feel I have a disorder in my breast that will cause troubles for my family in the future	3.31 (1-4)
5 I feel I have a problem in my breasts and this thought makes me anxious	3.31 (2-5)
6 I feel I have a problem in my breasts and this thought has disturbed my daily life	3.15 (2-5)
7 I feel I have a problem in my breasts and this thought disrupts my sexual activities	2.31 (2-3)
8 I need to obsessively examine my breasts to stay calm	2.38 (1-3)
9 I need to go for breast checkups sooner than my doctor has recommended for my peace of mind	1.62 (1-2)
10 I constantly search for and inquire about new methods for detection of breast disorders	2.00 (1-2)
11 I am constantly on the search for new information about breast diseases	2.00 (1-2)
LSQ-32	
1 I feel very often tired	3.46 (2-5)
2 I feel very often unfit	3.31 (3-4)
3 I often have difficulty sleeping	3.15 (1-5)
4 I often have a lack of appetite	1.31 (1-1)
5 I have frequent episodes of diarrhea	1.69 (1-2)
6 I have frequent episodes of constipation	2.08 (1-3)
7 I have frequent episodes of dizziness	1.92 (1-3)
8 I often have episodes of palpitations	2.77 (1-4)
9 I often have difficulty breathing	1.92 (1-3)
10 I often have muscle weakness	3.15 (2-4)
11 I often have pain	2.77 (1-4)
12 I often feel nauseous	1.85 (1-2)
13 I am very satisfied with my quality of life	3.62 (3-4)
14 I am very satisfied with my domestic situation	3.62 (3-5)
15 I am very satisfied with my economic condition	3.15 (3-4)
16 I do physical activity daily	2.23 (1-3)
17 I feel satisfied with the activities I do	3.46 (2-5)
18 I find the activities I do every day very interesting	3.38 (2-5)
19 I find very useful the activities that I do every day	3.23 (2-5)
20 I find the activities you do every day necessary	3.92 (4-4)
21 I find the family relationships I have very satisfying.	3.46 (3-4)
22 My family relationships vary constantly	3.77 (2-5)
23 I find my family relationships very enjoyable	1.85 (1-2)
24 I find my family relationships very important	4.08 (4-5)
25 I find my family relationships very independent of my life	3.85 (2-5)
26 I find my family relationships very pleasant	2.85 (1-4)
27 I find my friendships very satisfying	4.00 (4-5)
28 My friendships vary constantly	1.85 (1-2)
29 I find my friendships very important	3.85 (4-5)
30 I find my friendships very independent of my life	2.77 (1-5)
31 I find my friendships very pleasant	3.92 (3-5)
32 In general, I feel satisfied with my quality of life	3.38 (2-4)

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

Study conception and design: Vanni Gianluca, Materazzo Marco. Acquisition of data: Pellicciaro Marco, Meacci Arianna, Pizzimenti Anna Roberta; Analysis of data: Portarena Ilaria, Oreste Claudio

Buonomo; Interpretation of data: Vanni Gianluca, Materazzo Marco, Oreste Claudio Buonomo; Article draft: Vanni Gianluca, Materazzo Marco; Critical revision: Portarena Ilaria, Pellicciaro Marco, Pizzimenti Anna Roberta; Critical Revision of Literature: Buonomo Oreste Claudio.

References

1 Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, Vignat J, Gralow JR, Cardoso F, Siesling S, Soerjomataram I: Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast 66: 15-23, 2022. DOI: 10.1016/j.breast.2022.08.010

2 Buonomo OC, Morando L, Materazzo M, Vanni G, Pistilli G, Palla L, Di Pasquali C, Petrella G: Comparison of round smooth and shaped micro-textured implants in terms of quality of life and aesthetic outcomes in women undergoing breast reconstruction: a single-centre prospective study. Updates Surg 72(2): 537-546, 2020. DOI: 10.1007/s13304-020-00721-w

3 Buonomo OC, Grasso A, Pistolese CA, Anemona L, Portarena I, Meucci R, Morando L, Deiana C, Materazzo M, Vanni G: Evaluation of concordance between histopathological, radiological and biomolecular variables in breast cancer neoadjuvant treatment. Anticancer Res 40(1): 281-286, 2020. DOI: 10.21873/anticanres.13950

4 Materazzo M, Vanni G, Pellicciaro M, Anemona L, Servadei F, Giacobbi E, Farinaccio A, Pistolese CA, Perretta T, Chiocchi M, Bruno V, Tacconi F, Sadri A, De Majo A, Di Pasquali C, Meucci R, Santori F, Cotesta M, Buonomo OC: Case report: Early breast cancer recurrence mimicking BIA-ALCL in a patient with multiple breast procedures. Front Surg 8: 606864, 2021. DOI: 10.3389/fsurg.2021.606864

5 Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E: Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 30(8): 1194-1220, 2019. DOI: 10.1093/annonc/mdz173

6 Buonomo OC, Caredda E, Portarena I, Vanni G, Orlandi A, Bagni C, Petrella G, Palombi L, Orsaria P: New insights into the metastatic behavior after breast cancer surgery, according to well-established clinicopathological variables and molecular subtypes. PLoS One 12(9): e0184680, 2017. DOI: 10.1371/journal.pone.0184680

7 Vanni G, Pedini D, Materazzo M, Farinaccio A, Perretta T, Pistolese CA, Buonomo OC: Unusual presentation of a post-procedural breast hematoma: a case report. In Vivo 35(5): 2957-2961, 2021. DOI: 10.21873/invivo.12589

8 Vanni G, Materazzo M, Perretta T, Meucci R, Anemona L, Buonomo C, Dauri M, Granai AV, Rho M, Ingallinella S, Tacconi F, Ambrogi V, Chiaravalloti A, Schillaci O, Petrella G, Buonomo OC: Impact of awake breast cancer surgery on postoperative lymphocyte responses. In Vivo 33(6): 1879-1884, 2019. DOI: 10.21873/invivo.11681

9 Melaiu O, Vanni G, Portarena I, Pistolese CA, Anemona L, Pomella S, Bei R, Buonomo OC, Roselli M, Mauriello A, Barillari G: The combination of immune checkpoint blockade with tumor vessel normalization as a promising therapeutic strategy for breast cancer: an overview of preclinical and clinical studies. Int J Mol Sci 24(4): 3226, 2023. DOI: 10.3390/ijms24043226

10 Ferroni P, Roselli M, Spila A, D'Alessandro R, Portarena I, Mariotti S, Palmirotta R, Buonomo O, Petrella G, Guadagni F: Serum sE-selectin levels and carcinoembryonic antigen mRNA-expressing cells in peripheral blood as prognostic factors in colorectal cancer patients. Cancer 116(12): 2913-2921, 2010. DOI: 10.1002/cncr.25094

11 Ielpo B, Mazzetti C, Venditti D, Buonomo O, Petrella G: A case of metachronous splenic metastasis from renal cell carcinoma after 14 years. Int J Surg 8(5): 353-355, 2010. DOI: 10.1016/j.ijsu.2010.04.006

12 Kong X, Liu Z, Cheng R, Sun L, Huang S, Fang Y, Wang J: Variation in breast cancer subtype incidence and distribution by race/ethnicity in the United States from 2010 to 2015. JAMA Netw Open 3(10): e2020303, 2020. DOI: 10.1001/jamanetworkopen.2020.20303

13 Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, Cutter D, Darby S, McGale P, Taylor C, Wang YC, Bergh J, Di Leo A, Albain K, Swain S, Piccart M, Pritchard K: Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379(9814): 432-444, 2012. DOI: 10.1016/S0140-6736(11)61625-5

14 Malam Y, Rabie M, Geropantas K, Alexander S, Pain S, Youssef M: The impact of Oncotype DX testing on adjuvant chemotherapy decision making in 1-3 node positive breast cancer. Cancer Rep (Hoboken) 5(8): e1546, 2022. DOI: 10.1002/cnr2.1546

15 Noce A, Marrone G, Materazzo M, Vanni G: Editorial - Beyond breast cancer care: exploring pleiotropic effects of nutritional treatment for breast cancer patients. Eur Rev Med Pharmacol Sci 26(15): 5312-5315, 2022. DOI: 10.26355/EURREV_202208_29396

16 Syed YY: Oncotype DX breast recurrence score®: a review of its use in early-stage breast cancer. Mol Diagnosis Ther 24(5): 621-632, 2020. DOI: 10.1007/s40291-020-00482-7

17 Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351(27): 2817-2826, 2004. DOI: 10.1056/nejmoa041588

18 Sparano JA, Paik S: Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol 26(5): 721-728, 2008. DOI: 10.1200/JCO.2007.15.1068

19 Berdunov V, Millen S, Paramore A, Griffin J, Reynia S, Fryer N, Brown R, Longworth L: Cost-effectiveness analysis of the Oncotype DX breast recurrence score(®) test in node-negative early breast cancer. Clinicoecon Outcomes Res 14: 619-633, 2022. DOI: 10.2147/CEOR.S360049

20 Gormley M, Knobf MT, Vorderstrasse A, Aouizerat B, Hammer M, Fletcher J, D'Eramo Melkus G: Exploring the effects of genomic testing on fear of cancer recurrence among breast cancer survivors. Psychooncology 30: 1322-1331, 2021. DOI: 10.1002/pon.5679

21 Shubeck SP, Morrow M, Dossett LA: De-escalation in breast cancer surgery. NPJ Breast Cancer 8(1): 25, 2022. DOI: 10.1038/s41523-022-00383-4

22 Carlsson M, Hamrin E: Measurement of quality of life in women with breast cancer. Development of a Life Satisfaction Questionnaire (LSQ-32) and a comparison with the EORTC QLQ-C30. Qual Life Res 5(2): 265-274, 1996. DOI: 10.1007/BF00434748

23 Alipour S, Rashidi H, Maajani K, Orouji M, Eskandari Y: Development, validation, and implementation of a Short Breast Health Perception Questionnaire. BMC Public Health 22(1): 1060, 2022. DOI: 10.1186/s12889-022-13501-5

24 Kim JY, Lim JE, Jung HH, Cho SY, Cho EY, Lee SK, Yu JH, Lee JE, Kim SW, Nam SJ, Park YH, Ahn JS, Im YH: Validation of the new AJCC eighth edition of the TNM classification for breast cancer with a single-center breast cancer cohort. Breast Cancer Res Treat 171(3): 737-745, 2018. DOI: 10.1007/s10549-018-4858-z

25 Regione Lazio: Approvazione del documento tecnico regionale inerente alla "Procedura per l'esecuzione dei test genomici ormono-responsivo nelle pazienti con carcinoma mammario in stadio precoce", in attuazione del Decreto 18 maggio 2021 del Ministero della Salute. Boll Uff DELLA Reg LAZIO: 111-122, 2021. Available at: https://www.senonetwork.it/C_Common/Download.asp?file=/$Site$/files/doc/Documenti/normative-regionali/lazio/LAZIO_BUR-2021-88_TEST_GENOMICI.pdf [Last accessed on May 14, 2023]

26 Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, Lin NU, Perez EA, Goldstein LJ, Chia SKL, Dhesy-Thind S, Rastogi P, Alba E, Delaloge S, Martin M, Kelly CM, Ruiz-Borrego M, Gil-Gil M, Arce-Salinas CH, Brain EGC, Lee ES, Pierga JY, Bermejo B, Ramos-Vazquez M, Jung KH, Ferrero JM, Schott AF, Shak S, Sharma P, Lew DL, Miao J, Tripathy D, Pusztai L, Hortobagyi GN: 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med 385(25): 2336-2347, 2021. DOI: 10.1056/NEJMoa2108873

27 Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer CE Jr, Dees EC, Goetz MP, Olson JA Jr, Lively T, Badve SS, Saphner TJ, Wagner LI, Whelan TJ, Ellis MJ, Paik S, Wood WC, Ravdin PM, Keane MM, Gomez Moreno HL, Reddy PS, Goggins TF, Mayer IA, Brufsky AM, Toppmeyer DL, Kaklamani VG, Berenberg JL, Abrams J, Sledge GW Jr: Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379(2): 111-121, 2018. DOI: 10.1056/NEJMoa1804710

28 Orsaria P, Caredda E, Genova F, Materazzo M, Capuano I, Vanni G, Granai AV, de Majo A, Portarena I, Sileri P, Petrella G, Palombi L, Buonomo OC: Additional nodal disease prediction in breast cancer with sentinel lymph node metastasis based on clinicopathological features. Anticancer Res 38: 2109-2117, 2018. DOI: 10.21873/anticanres.12451

29 Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, Dinkel A, Butow P, University of Ottawa Fear of Cancer Recurrence Colloquium attendees: From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer 24(8): 3265-3268, 2016. DOI: 10.1007/s00520-016-3272-5

30 Fiszer C, Dolbeault S, Sultan S, Brédart A: Prevalence, intensity, and predictors of the supportive care needs of women diagnosed with breast cancer: a systematic review. Psychooncology 23(4): 361-374, 2014. DOI: 10.1002/pon.3432

31 Associazione Italiana di Oncologia Medica: I numeri del cancro in Italia, 2019. Available at: https://www.aiom.it/wp-content/uploads/2019/09/2019_Numeri_Cancro-operatori-web.pdf [Last accessed on December 18, 2021]

32 Vickberg SMJ: The concerns about recurrence scale (CARS): A systematic measure of women's fears about the possibility of breast cancer recurrence. Ann Behav Med 25(1): 16-24, 2003. DOI: 10.1207/S15324796ABM2501_03

33 Thewes B, Butow P, Bell ML, Beith J, Stuart-harris R, Grossi M, Capp A, Dalley D, FCR Study Advisory Committee: Fear of cancer recurrence in young women with a history of early-stage breast cancer: a cross-sectional study of prevalence and association with health behaviours. Support Care Cancer 20(11): 2651-2659, 2012. DOI: 10.1007/s00520-011-1371-x

34 Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, Ozakinci G: Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv 7(3): 300-322, 2013. DOI: 10.1007/S11764-013-0272-Z

35 van den Beuken-van Everdingen MHJ, Peters ML, de Rijke JM, Schouten HC, van Kleef M, Patijn J: Concerns of former breast cancer patients about disease recurrence: a validation and prevalence study. Psychooncology 17(11): 1137-1145, 2008. DOI: 10.1002/PON.1340

36 Koch L, Jansen L, Brenner H, Arndt V: Fear of recurrence and disease progression in long-term (≥5 years) cancer survivors-a systematic review of quantitative studies. Psychooncology 22(1): 1-11, 2013. DOI: 10.1002/PON.3022

37 de Jongh FE, Efe R, Herrmann KH, Spoorendonk JA: Cost and clinical benefits associated with Oncotype DX® test in patients with early-stage HR+/HER2- node-negative breast cancer in the Netherlands. Int J Breast Cancer 2022: 5909724, 2022. DOI: 10.1155/2022/5909724

38 Materazzo M, Facchini A, Garozzo D, Buonomo C, Pellicciaro M, Vanni G: Maintaining good practice in breast cancer management and reducing the carbon footprint of care: study protocol and preliminary results. World Cancer Res J 9: e2438, 2022. DOI: 10.32113/wcrj_202211_2438

39 Vanni G, Materazzo M, Pellicciaro M, Marino D, Buonomo OC: From patient reported outcome measure (PROM) to environment related outcome measure (EROM): Towards "Green Breast Surgery". In Vivo 37(4): 1867-1872, 2023. DOI: 10.21873/invivo.13278

40 National Institute for Health and Care Research Global Health Research Unit on Global Surgery: Reducing the environmental impact of surgery on a global scale: systematic review and co-prioritization with healthcare workers in 132 countries. Br J Surg 110(7): 804-817, 2023. DOI: 10.1093/bjs/znad092

41 Buonomo OC, Materazzo M, Pellicciaro M, Caspi J, Piccione E, Vanni G: Tor Vergata university-hospital in the beginning of COVID-19-era: Experience and recommendation for breast cancer patients. In Vivo 34(3 Suppl): 1661-1665, 2020. DOI: 10.21873/invivo.11958

42 Rita E, Chizoo E, Cyril US: Sustaining COVID-19 pandemic lockdown era air pollution impact through utilization of more renewable energy resources. Heliyon 7(7): e07455, 2021. DOI: 10.1016/j.heliyon.2021.e07455

43 Vanni G, Materazzo M, Dauri M, Farinaccio A, Buonomo C, Portarena I, Pellicciaro M, Legramante JM, Rizza S, Chiaramonte C, Bellia A, Grande M, Potenza S, Sbordone FP, Perrone MA, Grimaldi F, Chiocchi M, Buonomo OC: Lymphocytes, Interleukin 6 and D-dimer cannot predict clinical outcome in Coronavirus cancer patients: LyNC1.20 study. Anticancer Res 41(1): 307-316, 2021. DOI: 10.21873/anticanres.14777

44 Oldani C, Vanni G, Buonomo OC: COVID-19 unintended effects on breast cancer in Italy after the great lockdown. Front Public Health 8: 601748, 2020. DOI: 10.3389/fpubh.2020.601748

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