PERSONALIZED MEDICINE AT GLANCE: A REVIEW ON BREAST CANCER

Aniket Ugale[1], Mitesh Laddha[2], Abhishek Polshettiwar[3], Manthan Shirke[4], Satish Polshettiwar[5]*

ABSTRACT:
Breast carcinoma is the most prevalent category of malignancy in women globally. As breast cancer survivors and rescuers report a variety of health conditions which somehow impair their standard of living, the advancement of breast cancer treatment effective interventions while minimizing the potential negative consequences would be obligated.
Precision medicine in oncology aims to tailor almost every patient's rehabilitation regimen depending on it as an accurate assessment and management of tumor recurrence and maybe even advancement. Precision will always be successfully accomplished throughout every stage of medical services, from target identification to diagnostic testing to surgical intervention, interventional procedures, and radiotherapy, and finally high mortality or even supplementation actually give a damn.
Precision results from intimate analysis from each tumor's underlying biological proclivities, that instead of generalizing treatment programs predicated upon phenotypes or perhaps genetic variability categorization. Ongoing clinical strategy is evolving to accommodate the new perspectives, such as drifting away from categorizing large and diverse treatment methods into additional therapeutic comparability groups. The whole investigation encompasses several fields of clinical research investment. That very same special issue focuses on the analysis work of several parties concerned in precision medicine for breast cancer.

Keywords: Breast Carcinoma, Precision Medicine, Malignancy, Rehabilitation, Phenotypes,

[1,2,3,4,5]*School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Survey No.124, Kothrud, Pune, Maharashtra 411038 INDIA

***Corresponding Author:** Dr. Satish Polshettiwar
*E-mail: drsatishpolshettiwar@gmail.com,
Contact: +91-8796022838

INTRODUCTION:

The healthcare industry has experienced various changes as a result of in the 1860s The germ theory of disease was a challenging notion that was not broadly supported at the time the moment The first general anesthetics, chloroform and ether, had recently been implemented, allowing surgery With the ubiquitous usage of antiseptics, they are possibly life-saving rather than life-threatening was still several years distant. Medical problems, often referred to as non-diseases (NCDs), are the world's most important health problem in the 21th century. Carcinoma is one of the most common therapeutic targets, according to the World Health Organization (WHO). When malignancy is identified, most bodily tissue continues to develop and spread to other places of the body. Carcinoma can be both carcinogenic or – anti (benign). [1]

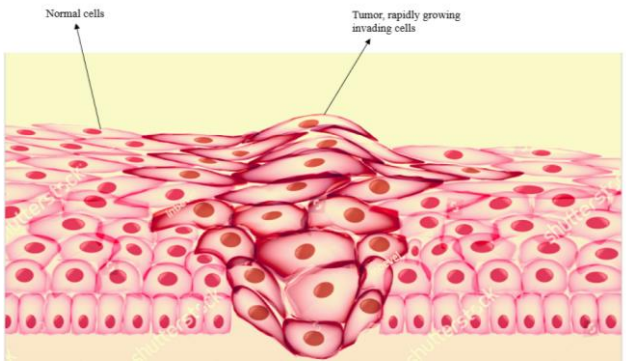

Fig 1: Tumor Cell

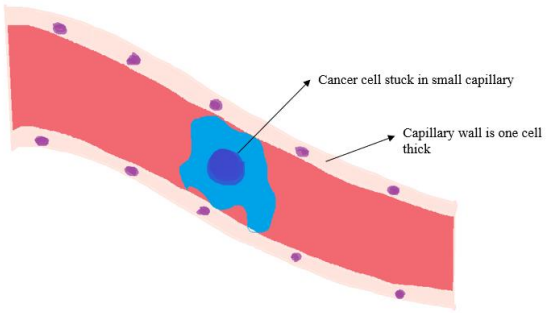

Fig 2: Cancer Stuck in small blood cell

Personalized medicine's ambition for the twenty-first century is to offer "the right medicine, at the right amount, with the right dose form, and the right route of administration, at the right time, to the right patient." In the healthcare and medical industries, precision medicine (PM) is a relatively new and exciting idea. It's a notion that has the ability to revolutionize medical treatments by offering effective, customized therapeutic solutions based on an individual's genetic, epigenomic, and proteomic profile, while also taking into account the patient's unique circumstances.[2]

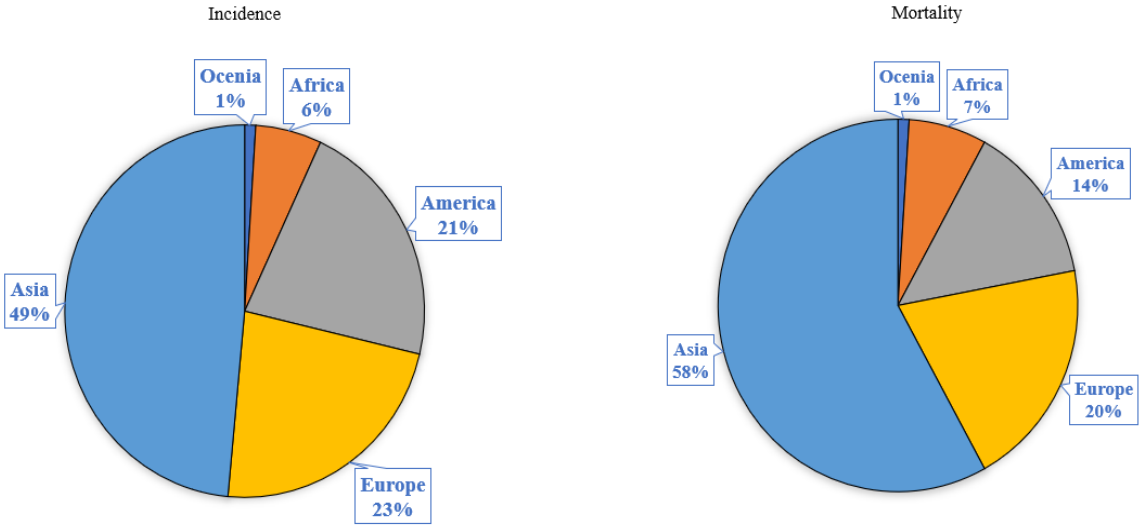

Fig 3: Pie chart of Cancer representing rate of (a) incidence (b) mortality

As per the literature we get to know in the above pie charts The occurrence, rate, or frequency of an illness is its incidence. Mortality, however, is the condition of being susceptible to death. Oceania has a 1% incidence rate, Africa has a 6% incidence rate, America has a 21% incidence rate, Europe has a 23% incidence rate, and Asia has a 49 percent incidence rate. On the other hand, Oceania has a mortality rate of 1%, Africa has a rate of 7%, America has a rate of 14%, Europe has a rate of 20%, and Asia has a rate of 58. It is the tallest in Asia.

Personalized medicine's ambition for the twenty-first century is to offer "the right medicine, at the right amount, with the right dosage form, and the right route of administration , at the right time, to the right patient." In the healthcare and medical industries, precision medicine (PM) is a relatively new and exciting idea. It's a notion that has the ability to revolutionize medical treatments by offering effective, customized therapeutic solutions based on an individual's genetic, epigenomic, and proteomic profile, while also taking into account the patient's unique circumstances.

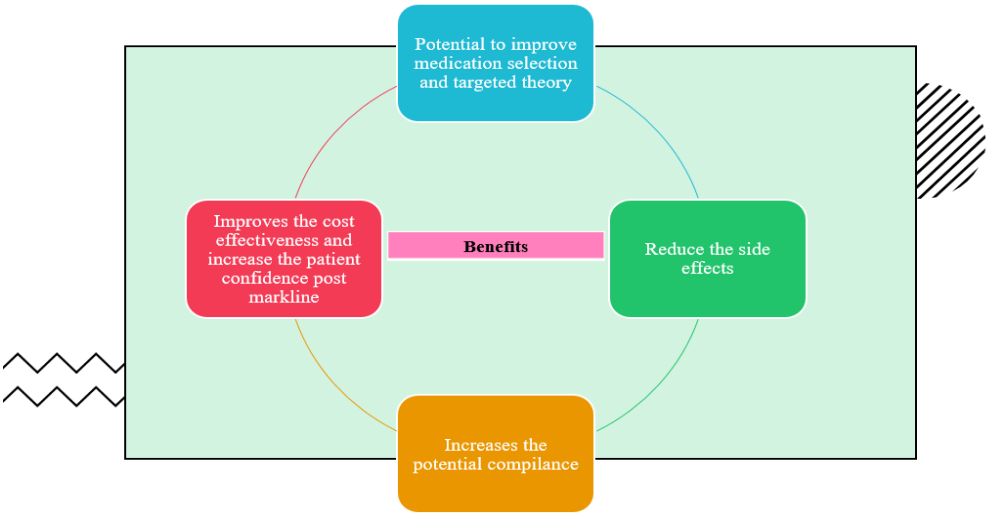

Fig 4: Benefits of Personalized medicine

1.1 Personalized medication therapies for breast cancer

Breast cancer is a disorder in which the cells of the breast get uncontrollably large. There are several types of breast cancer. The kind of breast cancer is determined by which cells in the breast become cancerous.

Breast cancer can start in a variety of places in the breast. Lobules, ducts, and connective tissue are the three primary components of a breast. The glands that generate milk are known as lobules. The ducts are tubes that transport milk from the breast to the nipple. Everything is held together by connective tissue, which is made up of fibrous and fatty tissue. Breast cancer usually starts in the ducts or lobules.

Breast cancer can spread to other parts of the body via blood and lymph arteries. When breast cancer spreads to other regions of the body, it's called metastasis. [3,4]

Kathrin Strasser and his associate members found that several preclinical women with breast cancer with female epidermal development factors receptors 2 (HER2) + status are presently not administered adjuvant anti-HER2 treatment because of resource limitations. They thought that identification of patient subgroups for which anti-HER2 TKI therapy may be advantageous. They utilized data from 2489 individuals with systemically diagnosed HER2+ illness. With the use of patient and tumor-related variables, they conducted subgroups evaluations and total count estimations. Patients on lapatinib who did not have a hormone receptor (HR-) had a noticeably longer illness life compared to HR patients on placebo. Starting therapy with lapatinib less than a year after diagnosis increased DFS for patients with HR- disease by 12.1 percent at two years and 15.7 percent at five years. [5]

David Cameron and his associate members took Trastuzumab, a conjugated monoclonal targeting the HER2 receptor, to prove that it dramatically increases survival rates and illness survival in women having HER2-positive early - stage breast cancer, through their clinical trial studies. HERA is a phase 3 randomized experiment that included 5102 HER2-positive early breast cancer patients from clinics in 39 different countries. It is a worldwide, multicenter, open-label trial. Patients were randomly randomized to obtain trastuzumab for one or two years after all first treatments were finished and the results were obtained that 1 year of adjuvant trastuzumab after chemotherapy for patients with HER2-positive early breast cancer significantly improves long-term disease-free survival, compared with observation. 2 years of trastuzumab had no additional benefit. [6]

Carolyn Cullinane and his associate members performed clinical trials to ascertain if ctDNA is associated with early, locally progressed, and metastatic breast cancer disease-free survival (DFS) and progression-free survival. The main finding was that ctDNA was associated with DFS, or relapse-free survival, in cases of breast cancer. Information across Eight investigations focusing on 739 individuals in total were appropriate. There was a statistically significant correlation between shorter DFS and the identification of circulating tumor DNA gene variation (both before and after therapy). The DFS was statistically substantially lower in the early breast cancer subgroup and the metastatic or locally progressed subgroup when ctDNA was detected. Plasma sample collection before and after therapy was examined in early and metastatic groups. Both surgical and oncologic treatments were included in the posttreatment group. The DFS was statistically substantially correlated with pretreatment plasma ctDNA detection. CtDNA posttreatment sample was not statistically significant. [7]

Safa Najafi and associate members found that the patients with breast cancer frequently experience nausea and vomiting brought on by chemotherapy (CINV). Their study's objective was to evaluate the effects of dietary counseling on PsBC patients' CINV and quality of life. In order to lessen the severity of CINV before each chemotherapy session for three times, 150 PsBC were randomly assigned to receive either a personalized diet containing 1.2-1.5 g/kg of protein, 30% of energy from fat, and 55-60% from carbohydrates, a face-to-face nutrition education session, and a pamphlet containing helpful nutrition information. Each chemotherapy session was followed by an evaluation of CINV, QoL, and food intake. The intervention group had noticeably decreased nausea rating index, total nausea index, and visual analogue scale (P 0.001). Musculoskeletal performance, social ability to operate, psychological well being, cognitive ability to function, and overall health status/quality of life (P 0.001) were all significantly improved in the treatment condition. More tiredness, nausea and vomiting, discomfort, dyspnea, lack of appetite, constipation, and diarrhea were reported by patients in the control group (P 0.001). Adjuvant chemotherapy for PsBC patients who received nutritional counseling decreased the incidence of CINV and significantly enhanced QoL. [8]

Susanna M Wallerstedt and associate members evaluated the data needed to make judgments on the use of gene expression tests to guide chemotherapy choices in breast cancer patients with medium clinical probability of relapse at the patient and healthcare provider levels. OS and recurrence were evaluated with and without a gene expression test in three inconclusive non-RCTs. One RCT and four non-RCTs investigated OS in relation to the comparison of withholding versus administering chemotherapy based on a gene expression test. In the RCT, 93.9% of the I group and 93.8% of the C group were still alive at nine years. Recurrence was assessed in three RCTs and seven non-RCTs. The result obtained showed that the comparison of three RCTs revealed that 4.29 percent versus 3.88 percent of cases of distant recurrence occurred.[9]

Yi-Zhou Jiang and associate members found that due to the substantial heterogeneity of triple-negative breast cancer (TNBC), molecular subtyping may help with more accurate diagnosis and tailored treatments. TNBCs were divided into four subgroups in our earlier work, each of which had potential therapeutic targets. In order to assess the effectiveness of these targets, they carried out the FUTURE study, a phase Ib/II subtyping-based and genomic biomarker-guided umbrella trial. Patients with refractory metastatic TNBC were enrolled, stratified by genomic biomarkers and TNBC subtypes, and randomly assigned to one of seven treatment arms: (A) capecitabine with pyrotinib; (B) androgen receptor inhibitor with CDK4/6 inhibitor; (C) anti-PD-1 with nab-paclitaxel; (D) PARP inhibitor included; (E) and (F) anti-VEGFR included; or (G) mTOR inhibitor with nab-paclitaxel. The objective response rate was served as the primary endpoint (ORR). With a median of three prior lines of treatment, we included 69 patients with metastatic TNBC. Of the 69 intention-to-treat (ITT) patients, 20 had an objective response. Their findings demonstrated that in the ITT group, immunotherapy (arm C) in particular had the greatest OR. Positive ORR was seen in Arm E, however there were higher grade (3) adverse events. In the immunomodulatory subtype of TNBC, somatic TOP2A and CD8 immunohistochemistry score mutations may be able to predict the efficacy of immunotherapy. To conclude, the phase Ib/II FUTURE study offered a fresh idea for treating TNBC by showcasing the therapeutic advantage of subtyping-based targeted therapy for metastatic TNBC that is resistant. [10]

1.1.1 Breast cancer biomarkers and subtypes

Breast cancer is a difficult disease to understand the diagnosis. Relying on the immunohistochemistry (IHC) variants [e.g. estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2)], melanoma has distinct prognostic value and responses to chemotherapies. HR-positive (ER and/or PgR-positive) but not HER2-positive breast tumors react well to hormone therapy and have a reliable outcome. Triple-negative (TN: ER, PgR, and HER2-negative) breast tumors have quite a poor prognosis initially and respond effectively to HER2-targeted medication and psychotherapy. The first biochemical subtypes of breast cancer (luminal A, luminal B, HER2-enriched, and basal) were identified in 2000.Examining sequences of mRNA expression in 65 laparoscopic biopsies of human breast cancer demonstrated that each illness had a unique molecular subtype. [11 12]

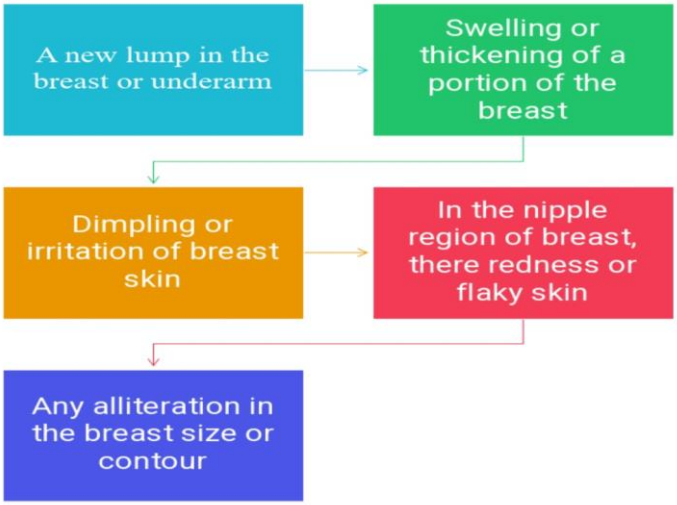

Fig 5: Stages of breast cancer

So every illness was identified by the sequences of expression levels in 65 intraoperative biopsies of various cancer cell lines. HR-positive/HER2-negative cancers are classified as luminal A or B according to their malignant grade. This distinction is used to judge the appropriateness of methotrexate. In HR-positive/HER2-negative tumors, gene regulation sequences were being used to improve molecular criteria that may have outperformed established pathological biomarkers. Considering such studies, it was proposed that all subtypes have their own biomarkers. In the 1980s, D. Perou found chromosomal subtypes. Furthermore, a number of novel next-generation biomarkers for early-stage breast cancers in the perioperative period have just been developed following IHC ER, PgR, and HER2. [13] [14]

1.1.2 First-era genomic signature

For HR-awesome/HER2-lousy and node-lousy breast most cancers, numerous first-era genetic markers strongly related to the mobileular cycle and proliferation had been identified. Two of them (Oncotype DX, Genomic Health's 21-gene recurrence rating, and MammaPrint, Agendia Inc.'s 70-gene signature) had been investigated in capability randomized and managed research to see if they'll count on assessment and remedy reaction. They're turning into extra now, not an unusual place in clinical practice. Despite the minimum overlap of genes, first-era genomic signatures exhibited comparable usual performance.Another tough problem is the feature of the first-era signature in HR-awesome/HER2-lousy and node-awesome breast cancer. Breast most cancers nodal popularity is a prognostic however no longer a predictive indication. Patients with HR-awesome and node-awesome breast most cancers ought to often get each hormone remedy and chemotherapy, because of the truth they've got a horrible assessment no matter chemotherapy sensitivity. In a retrospective facts set of 367 sufferers with breast most cancers, Albain et al. located that the 21-gene recurrence rating is prognostic for hormone-handled node-awesome sufferers and predicts a huge advantage of chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil in breast cancers with a excessive recurrence rating. In a retrospective evaluation of a prospectively set up research, Stemmer et al. located that sufferers handled with N1 (1–three awesome lymph nodes) with a recurrence rating of 18 who underwent hormone remedy by myself had a five-one year DFS of 2.7 percentage (ninety five percentage CI, 1.4–five.1 percentage). [15] [16]

1.2 PERSONALIZED TREATMENT

Precision medicine is a wide term that refers to a variety of clinical and fundamental scientific areas. True therapy customization would consider a person's genes and genetic disposition, breast tissue composition, overall "omics" profile of their cancer and associated biologic propensities, tissue microenvironment, concomitant diseases, lifestyle, patient desire, and quality of life. Precision medicine is used in the preventing and detecting of cancer even before it is diagnosed. Precision medicine requires a fundamental change in traditional diagnostic testing upon diagnostic test, as relatively small bins of mechanistically staged patients undergoing novel targeted agencies does not provide sufficient numerical capacity to identify significance for traditional definitions of outcome endpoints like local democracy or overall survival. [17] [18]

The Precision Medicine Initiative was started in Jan 2015 by the Obama administration in the US with the goal of improving the treatment and cure of illnesses such as cancer, which is the initiative's near-term disease emphasis. This cancer-specific component is intended to address current hurdles to attaining precision cures, such as medication resistance, tumor genetic heterogeneity, accurate tumor response indicators, and the most effective approaches for combining several medicines or modalities. Over a million people's data will be collected, and pilot tests of treatments and longitudinal studies of outcomes will be done. Because data will be readily shared with research, clinicians, and the general public, this major federally funded programmed promises to speed precision medicine developments more broadly. In the precision medicine era, breast cancer awareness is very well poised to achieve major breakthroughs. There has already been a lot of preparation. The work being done to attain personalized medicine objectives in tumor detection, protection, diagnosis, and therapy is highlighted in this special issue. [19] [20]

Precision Medicine Disciplines in Breast Cancer
1.2.1 Screening Diagnosis

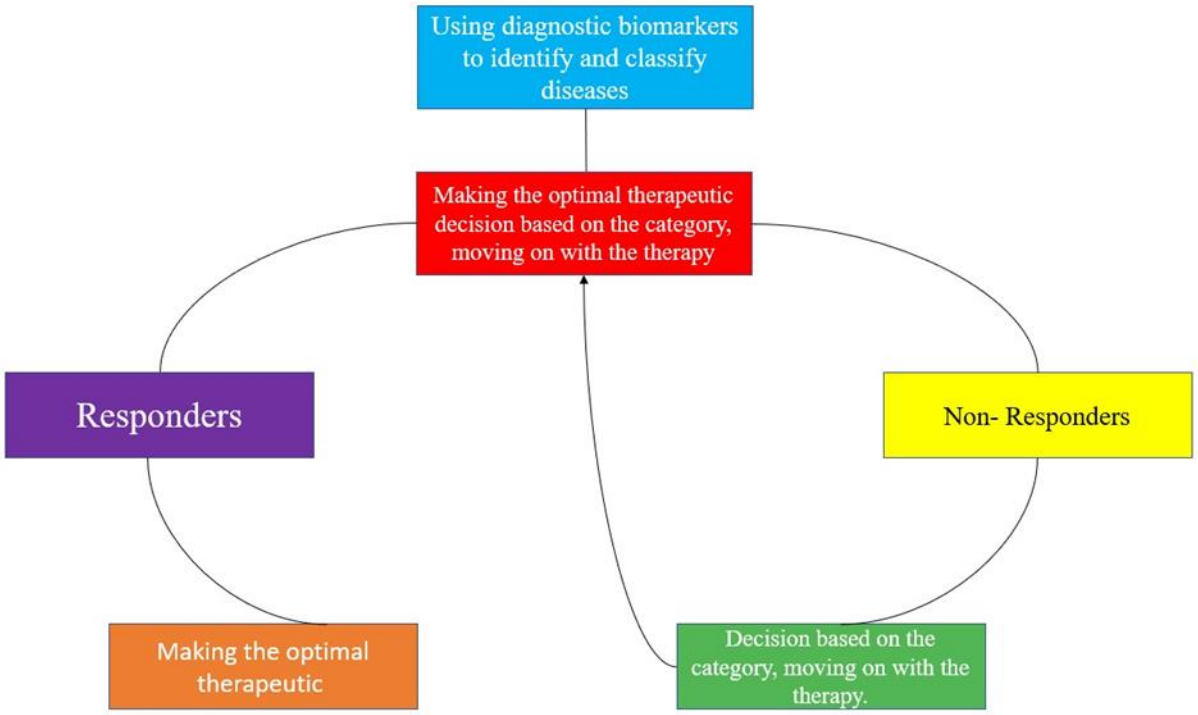

Fig 6: Screening Diagnosis in breast cancer

It may also reduce under screening, especially among the younger population, where early diagnosis is more difficult but probably more important in terms of results. Low-risk patients may be screened less frequently or not at all, saving money and avoiding needless testing owing to false positive findings.[21] Patients with a high risk of developing cancer might start screening earlier, have it done more frequently, or incorporate functional imaging such as an MRI. Clinical studies are now being conducted to investigate risk-based screening.[22] [23]

Risk stratification methods are being revised in the general screening population. Breast density has been recognised as a major risk factor for cancer development. Breast density is categorized into four for use in screening mammography interpretation by the Breast Archiving and Reporting Data System (BIRADS): fatty, scattered fibrous cellular concentrations, highly heterogeneous dense, and very dense. In a massive Swedish mammographic screening study of over 15,600 women aged 45 to 59 who have been followed for 25 years, dense breast tissue was connected to a 1.57 adjusted odds ratio risk of cancer incidence and a 1.9 relative risk of breast cancer death. The Breast Cancer Surveillance Consortium used the SEER database to perform a case control study and prospective risk factor collecting from their registry of breast imaging facilities from 1996 to 2012, reporting the BI-RADs breast density, among other risk variables. When adopting an objective of population attributable hazard proportion of acquiring breast cancer, breast density was the most common prediction for all age groups.[24] [25] The BMI (body mass index) was also important. As a result of these issues, researchers are conducting studies to determine the ideal time, regularity, and scanning methods for monitoring women having dense breasts, that might include investigations such as MRI. Breast density was used in the risk assessment algorithm for the first time by the Breast Cancer Surveillance Consortium. Diet, nutritional supplements, exercise, and pharmacologic treatments have all been studied as ways to lower breast density. The influence of lifestyle treatments such as good eating, weight loss, and physical activity on lowering breast cancer incidence might be significant.[26]

In terms of customizing radiation for breast cancer, there are various areas of interest.One of the primary goals is to avoid overtreatment of low-risk individuals whose tumors do not satisfy the 10–20 percent probability of local recurrence necessary for breast radiation to be beneficial in terms of survival. Several multi-institutional studies using gene arrays to identify individuals for observation (no radiation) after breast conserving surgery are now being conducted. The PAM50 ROR is used in the Precision trial to

identify phase I breast cancer patients for removal of radiation after lumpectomy, whereas the Oncotype DX Recurrence Score is used in the IDEA research. [27]

1.2.2 Molecular Subtype and Systemic Therapy

There are chemical subgroups of breast cancer that define phenotypic behaviors based on genetic determinants. However additional research is needed due to the high variation both within and between these subtypes. The general method for diagnostic characterization of any and all women with breast cancer uses immunohistochemistry testing, and molecular subtyping is one of the key factors in therapy selection. Perou et al. used the DNA microarray approach for data study of the patterns of gene expression in over 8000 genes to identify "molecular pictures" using 65 breast cancer cases. Based on the variations in the expression profiles, these patterns were divided into subtypes. [28] [29]

Based on this landmark study and additional research, the following categories represent the most prevalent general molecular subtypes at present: Her2 enhanced (ER critical, PR negligible, and Her2 positive); triple negative/basal-like; and luminal A (estrogen receptor (ER) positive, Her2 negative, AND Ki-67 low 14 percent, OR Ki-67 intermediate 14-19 percent, and progesterone receptor (PG) high > 20 percent); luminal B (ER productive, Her2 negative, AND Ki-67 intermediate 14-19 percent, and PG low/negative OR Ki-67 high > 20 percent, OR Her2 (ER negative, PR negative, and Her2 negative).[30] The easiest and most accessible technique is to employ these immunohistochemistry tests to determine the expression pattern (with FISH testing in situations where Her2 is ambiguous). The characteristics that result from the molecular subtypes are correlated with tumor behavior, prognosis, and therapeutic response. [31] [32]

On tumor tissue, a 70-gene array of gene transcription is also examined, as well as its gene panel comprising pathways for growth stimulation, death, replicating, metastases, and vasculature. For a wider set of breast tumors, even those with Her2-positive plus nodal positive tumors, the test delivers an excellent or poor prognostic signal that distinguishes among risk of distant metastasis.[33] Similar to the 21-gene assay, it is applied therapeutically to direct use of such systemic chemotherapy or, occasionally, to provide additional prognosis in women having moderate recurrence scores. Prediction Analysis of Microarrays (PAM50, Prosigna, Nanostring Technology) is a 50-gene mRNA expression array that was created to categorize intrinsic molecular subtypes. [34] [35]

Risk of recurrence (ROR) score, a predictive value provided by the test, was developed from the trial of early phase ER positive/Her2-negative postmenopausal individuals treated with endocrine treatment in relation to overall responsiveness to preoperative or postoperative chemotherapy. [36] Triple negative breast cancer accounts for up to 20% of invasive breast cancers and constitutes a diverse collection of subtypes further identified by other molecular markers. Most of these subgroups are among the most aggressive and have a terrible prognosis in breast cancer, while others have a reasonably decent prognosis.[37] New biomarkers for triple-negative cancer association are being researched. Although the phrase "basal-like" is not defined, it often refers to breast tumors with certain gene expression patterns, such as absence of ER, PR, and Her2 expression, expression of basal cytokeratins (CK5/6, 14, or 17), and/or EGFR. In addition, these tumors frequently have high mitotic indices, lymphocytic infiltrates, necrotic or fibrotic regions, and are high grade.[38] Although the majority of basal-like tumors also fall into the quintuple category, there are some differences between the two classifications. Cancers developing in BRCA1 germline mutation carriers have a known association with basal-like lesions. Researchers are using "omics" technologies to further classify this high risk class of breast tumors, which have identified at least 6 triple negative subtypes based on gene expression, molecular pathways, and responsiveness to treatment drugs.[39] Such sophisticated diagnoses require enormous amounts of data and validation in clinical trials that can examine outcomes in such tiny subgroups of patients. Although the majority of basal-like tumors also fall into the quintuple category, there are some differences between the two classifications. Cancers developing in BRCA1 germline mutation carriers have a known association with basal-like lesions.[40] Researchers are using "omics" technologies to further classify this high risk class of breast tumors, which have identified at least 6 triple negative subtypes based on gene expression, molecular pathways, and responsiveness to treatment drugs. Such sophisticated diagnoses require enormous amounts of data and validation in clinical trials that can examine outcomes in such tiny subgroups of patients. I-SPY 2 is a unique clinical study that employs pathologic response to neoadjuvant chemotherapy as the primary objective to evaluate the safety and

effectiveness of investigational medicines in stage II-III patients.[41] The results of combining the anti-PD1 antibody pembrolizumab with chemotherapy in Her2-negative patients were presented at the ASC0 2017 annual meeting and revealed that triple negative patients had the highest pathologic complete response rate of 40% among all Her2-negative patients, showing an improvement in response when compared to chemotherapy alone.[42] While objectives such as pathologic response must eventually transfer into overall survival benefit, this unique trial design has enabled for more quick assessment of molecular data as well as response to medication to inform future research.In response to the identification of actionable mutations, many kinds of targeted medicines are being researched. Over 70 medicines have been licensed for the treatment of breast cancer, and they are used in a variety of sequences and combinations. Immunotherapy agents are of particular interest.[43] [44] A contemporary strategy employs monoclonal antibodies that disrupt immune suppressive proteins such as CTLA-4 and PD-1/PD-L1. Several clinical trials with immune agents such as nivolumab, pembrolizumab, and atezolizumab in advanced or metastatic breast cancer have been completed and show promise, albeit complicated interactions between the tumor immunological milieu, host immune system, and timing of therapy require substantial more research before widespread clinical usage. [45] Immune modulators are ineffective as single treatments and are frequently used in combination with other cytotoxic drugs.[46] In restricted, or oligometastatic, illness, one interesting method includes using ablative radiation doses to an index lesion to activate host immunity through improved antigen presentation in conjunction with immunotherapeutic drugs. [47] [48]

1.2.3 Radiomics

On tumor tissue, a 70-gene array of gene transcription is also examined, as well as its gene panel comprising pathways for growth stimulation, death, replicating, metastases, and vasculature. For a wider set of breast tumors, even those with Her2-positive plus nodal positive tumors, the test delivers an excellent or poor prognostic signal that distinguishes among risk of distant metastasis. Similar to the 21-gene assay, it is applied therapeutically to direct use of such systemic chemotherapy or, occasionally, to give additional prognosis in women having moderate recurrence scores. Prediction Analysis of Microarrays (PAM50, Prosigna, Nanostring Technology) is a 50-gene mRNA expression array that was created to categorize intrinsic molecular subtypes. Risk of recurrence (ROR) score, a predictive value provided by the test, was developed from the trial of early phase ER positive/Her2-negative postmenopausal individuals treated with endocrine treatment in relation to overall responsiveness to preoperative or postoperative chemotherapy. There are other more gene assays in use or being validated. The greatest level of evidence presently supports the use of either the PAM50 ROR or the Oncotype DX Recurrence Score, according to the most recent American Society of Clinical Oncology (ASCO) recommendation. Radiomics may help in screening, diagnosis, treatment planning for radiation or surgical procedures, assessing therapeutic response, and follow-up care. If radiomic features are correctly verified, they may assist in identifying the tissue at risk for radiation target volume delineation, eliminate biopsies or surgery, and differentiate post treatment results to tailor workup and treatment for recurrence. [49]
Utilizing quantitative characteristics from medical pictures in prognosis or prediction algorithms that are connected with pathology, genetics, or clinical outcomes is the developing discipline of radiomics. Such characteristics might be created in the context of breast cancer screening to tailor the frequency or mode of screening based on more specific risk factors. It is hoped that a combination of genetic subtyping and functional imaging tests will help distinguish between aggressive and passive phenotypes. Tomosynthesis, contrast-enhanced mammography, and MRI are some of the imaging techniques being researched. To differentiate among DCIS and invasive lesions, high - spatial MRI may evaluate the features of the lesion, potentially reducing the need for additional counseling and testing of the lower risk solely intraductal lesions. Utilizing statistical characteristics from healthcare pictures in prognosis or prediction algorithms that are connected with pathologies, genetics, or clinical outcomes is the developing discipline of mammography. Such characteristics might be created in the context of breast cancer screening to tailor the number or mode of testing based on more specific risk factors. It is hoped that the role of genetic subtyping and functional imaging tests will help distinguish between aggressive and passive traits. Tomosynthesis, contrast-enhanced mammography, and MRI are some of the imaging techniques being researched. [50]

CLINICAL TRIALS:

Clinical trial data is helping to refine target volume personalization: whole or partial breast; nodal volumes or none; which nodal levels. It is, however, possible to fine-tune desired values even further. Current procedures use anatomic signals such Computed tomography breast tissue or even the surgery bed plus a constant extension margins, as well as clinical and pathological characteristics, to characterize the risk of local-regional recurrence.

Country ➜ / Number of trails ↓	INDIA	USA	UK
Number of clinical trials performed	10	10	2
Number of clinical trials completed	6	5	0
Number of clinical trials ongoing	4	3	2

Table 1: Number of clinical trials performed between 2019-2022 in India,USA, & UK

PERSONALIZED MEDICINE CARE FOR BREAST CANCER AND METASTATIC CANCER

People with metastatic BC are treated differently according to their age, menopausal status, functional level, comorbidity, disease-free interval, past therapy, and the location and number of metastases. In addition, the main biological approaches presently employed in HER2 expression assessments are included in adjuvant settings just like they're in adjuvant situations. Every day is a rehearsal.

There is, however, no clear cut off point for preventing HT activity. This is why when at least 1% of cancer cells are stained, HT can be indicated. Currently, there is no biological component. Another factor to take into account seems to be that HR activity has been connected to partial resistance to chemotherapy. Trastuzumab, epratuzumab, and in situ findings determine the effectiveness of trastuzumab, epratuzumab, and lapatinib. It's worth mentioning that in the past, HER2 overexpression was connected with HT tolerance in HR-positive cancers. In this cohort, however, the advantages of HT are not negligible, indicating that it should be used for individuals with HER2-positive HR-positive cancers. However, the dilemma of whether HR as well as HER2 status should be tested at the primary tumor or at the metastatic location emerges. Treatment strategies regarding metastatic individuals were previously focused on the molecular features of the primary tumor. More recent retrospective investigations have shown HR and HER2 expression both in primary and recurrent malignancies. Possible causes include methodological bias, tumor heterogeneity, and clonal selection. There had been a two-fold increase in the risk of mortality when comparing individuals either with or without ER loss. The study included 182 HER2-positive participants. There is a decreased likelihood of survival, especially in situations where there's been a previous CT. This is the demographic. 789 recurring illnesses were studied by Liedtke et al. In 231 BC patients, ER, PR, and HER2 levels were measured. Furthermore, these modifications were made in a timely manner. It has been linked to a lower outcome. The writers recommended there are two possibilities. First, the lower outcome could be caused by pathogenic exploration, which could result in incorrect diagnosis and treatments due to measurement bias. Second, a true shift in tumor phenotype could lead to more aggressive activity, resulting in a worse prognosis. In a retrospective comparison analysis of 200 patients with liver metastases, Botteri found that survival was equal with or without liver metastasis. However, 18 of the 100 biopsied patients had phenotypic alterations that necessitated therapeutic changes. These patients fared better than other biopsied individuals in terms of survival. The outcomes of metastatic biopsy, including the impact on survival, were recently published in a prospective trial. Eighty percent of the 121BC with metastases had their metastases pathologically examined at the time of diagnosis. % Of patients had their treatment altered. Patients with phenotypic disparity did not have a worse prognosis after a year, possibly due to therapeutic adjustments in this cohort. These findings have subsequently been verified in a meta-analysis. Finally, in circumstances where the diagnosis is in dispute, such as distinct lesions, a history of many initial malignancies, or ambiguity following clinical and

radiological tests, a metastatic biopsy is advised to confirm the diagnosis. If the biopsy procedure is thought to be safe, it should be used to confirm the diagnosis and monitor HR and HER2 expressions in the future. Despite this, because of the potential for tumor heterogeneity, halting targeted therapy in the case of loss of expression in secondary tumors is not yet suggested. As a result, pathological investigation of metastases is more often employed to add new therapy choices than to reject old ones. Non-invasive methods are being studied to prevent the risks and pain of biopsies, as well as the failures or mistakes that can occur due to tumor heterogeneity. Cell search, the only technology approved by the FDA, can be used to identify and quantify circulating tumor cells. It is based on the identification of CD45-negative epithelial cells in peripheral blood with cytokeratin positive staining. High CTC levels are linked to a poor outcome in metastatic BC patients. In retrospective investigations as well as major prospective research, CTC's prognostic and predictive abilities have been established. Even though Cell Search has been approved by the FDA, it has yet to be authorized by the European Medical Agency, as ASCO does not suggest using it in daily practice. However, innovation has yet to have a long-term beneficial impact on survival or life quality. The French STIC designed the META BREAST trial to demonstrate that CTC identification is not inferior to PFS and that the CTC arm is superior in overall cost efficiency evaluation. The trial will involve 994 individuals with metastatic BC who are HR positive but HER2-negative. Patients are separated into two groups: those who receive treatment based on the clinician's decision and those who receive medical treatment based on the CTC evaluation. Patients in the CTC arm will get CT, while people with fewer than 5 cells per 7.5 mL will receive HT. Early alterations of CTC numbers during chemotherapy are the subject of two other investigations. The primary outcome of the SWOG S0500 experiment was a higher CTC frequency after the first cycle, which was compared to treatment adjustment guided by conventional clinical and radiological features. The CTC phenotype is also a viable option. Patients with HER2-negative metastatic BC and at least one HER2-positive CTC/7.5 mL are eligible for the DETECT III study. The patients are randomly assigned to receive normal therapy or the same compounds as lapatinib. PFS is the primary goal. The use of high-throughput technologies to profile circulating tumor DNA is also being investigated. In a prospective study, fifty-two metastatic BC individuals were matched to various surveillance methods: CTDNA, imaging, CA 15-3 serum levels, CTC count, genetic abnormalities found in tumor tissue, and, in a prospective study, almost all of the patients showed genetic alterations in their tumor tissue. It was discovered that CTDNA contained 97 percent of these alterations, which could be discovered using digital PCR or labeled amplicon deep sequencing technologies. alterations were better connected to tumor modifications in this population than CTC or CA 15-3 changes. Following that, the same researchers demonstrated that CTDNA deep sequencing may discover mutations associated with chemotherapy resistance. Our understanding of BC has been transformed by the use of microarray technology. Next-generation sequencing is another method that also assists in understanding BC better. It allows for the simultaneous sequencing of several genes, ranging from tens to the entire genome. Depending on the length of the amplicons being investigated, results might take 1–15 days. This novel sequencing technology can detect known and undiscovered mutations and is quicker and less costly than the classic Sanger method. Even though FFPE specimens can be utilized for a limited number of gene analyses, the majority of examinations are still performed on frozen samples. This new method also enhances data flow, requiring new bioinformatics tools to respond. Only a small percentage of NGS in BC has indeed been described. These genes are commonly found in biochemical functions that are comparable, including several that are implicated in endocrine drug resistance. The creation of specialized medicines is the next step after the identification of several rare abnormalities. Hundreds of targeted drugs are being researched individually and in combination. This new concept would make the standard clinical trial approach, which involves creating a medicine for the entire population and then looking for predictive biomarkers, obsolete. Patients will be directed to dedicated early-phase trials using new methodologies based on tumor genetic profiles. These studies will be shorter, cheaper, and, ideally, use more effective medicines because they will be focused on small populations. A variety of methods can be used to identify biological changes. Genomic instability, DNA damage response changes, and susceptibility to PARP inhibitors have all been associated with genetic variants, translocations, and point mutations. Amplifications, translocations, and genetic abnormalities have all been associated with genomic changes. 86 individuals with resistant metastatic tumors were

investigated by Von Hoff et al. They used IHC and gene expression profiling to assess the expression of 61 genes. In 84 patients, one putative target was found, and 66 got genome-guided therapy. Eighteen individuals experienced approximately 1.3-fold longer PFS than patients who received the prior treatment line. Similarly, 40.2 percent of phase 1 study participants at MD Anderson Cancer Center had at least one genetic mutation. Patients who received matched treatments had a higher overall accuracy, a much longer time to treatment failure, as well as a longer overall survival time. SHIVA is a randomized phase II proof-of-concept trial targeting individuals with resistant solid tumors in France. A molecular profile of the disease is generated from a tumor sample using IHC, array-CGH, and decoding of 46 genes utilizing Ion Torrents. If a molecular change is found for which an authorized targeted medicine is available in the trial, patients are randomly assigned between chemical characteristic treatment and conventional therapy depending on the investigator's preference. PFS is the main outcome after randomization. Patients must be screened in order to randomize 200 occurrences of vemurafenib, sorafenib, erlotinib, trastuzumab, lapatinib, dasatinib, tamoxifen. This method has also been used to study metastatic BC. UNICANCER's French SAFIR01 prospective study enrolled 423 patients over the course of 16 months. Array-CGH and mTOR pathway gene sequencing were used to examine the pathology of metastases. The patient was referred to a specific early-phase clinical study when a molecular targetable abnormality was discovered. In 64% of patients, a tumor molecular profile was discovered, with 69 percent having one or more targetable alterations. The preliminary data revealed that 26 people had received focused therapy, with eight of them seeing therapeutic benefits. The MOSCATO study duplicates the SAFIR01 design in advanced solid tumors. The developing concept of intra-tumoral heterogeneity is one of the primary challenges of this biopsy-driven therapeutic targeting. The adverse effects of modern cancer therapies lower the QOL for cancer patients who are receiving chemotherapy: Current cancer therapies, such as chemotherapy, have been shown to cause unfavorable cancer-related symptoms in breast cancer patients, lowering their quality of life. A previous study looked at the symptoms experienced by breast cancer patients during chemotherapy and discovered 38 common symptoms classified into five consistent symptom clusters. Chemotherapy's impact on symptom experience and quality of life in breast cancer survivors It entails assessing these people's emotional and physical well-being at several points during their lives, and also before therapy, after cycle 3 of chemo, within 2–3 weeks after ending supplemental chemo, and at least eight years following treatment. Despite the fact that no clear deterioration in cognitive performance was found, the authors stated that patients' depressive symptoms and weariness intensified. In Improving the Quality of Life of Patients Undergoing Chemotherapy: Administration of chemotherapeutic medications is frequently connected with the occurrence of unpleasant side effects that significantly affect cancer patients' QOL and performance status. In light of this, personalized medical procedures should not be limited to enhancing the overall efficacy of the therapeutic process. [51] [52]

They should also consider how to develop medicines that target the aforementioned side effects of cancer therapy. We discuss the findings that could aid in the development of novel consultations for women with breast cancer to improve their quality of life, with a focus on how our current understanding of genomic information and metabolomics could aid in the development of personalized interventions to improve the QOL of women with breast cancer both during and after chemotherapy treatment.

1. CIPN (Chemotherapy induced peripheral neuropathy) selection:

Many genetic indications connected to CIPN have also been discovered recently, offering valuable insights into just how chemotherapy drug-induced neurotoxicity might be reduced and controlled in cancer patients undergoing chemotherapy. The 3435 TT genotype of ABCB1, a gene which codes for an ATP-binding cassette subfamily protein, has been identified to enhance the incidence of neurotoxic reactions in breast cancer patients following paclitaxel or docetaxel therapy. Similarly, the gene coding for a Charcot-Marie-Tooth protein, NDRG1, has been recommended as a genetic biomarker for CIPN due to a negative connection between its expression level and the severity of the disease. Furthermore, carriers of the CYP2C8*3 and/or FGD4 c.2044–236 G > A polymorphism has been shown to have a greater risk of CIPN, prompting early paclitaxel dosage reduction in these patients. Overall, the aforementioned genes can be employed as new gene targets for tackling chemotherapeutic drug-induced neurotoxicity, which might aid in the development of interventional approaches for CIPN treatment. [53] [54]

2. Targeting the cognitive dysfunction:
Chemotherapy treatment was once assumed to be a cause of cognitive loss in cancer patients. Although the exact process of inflammation remains unknown, according to a recent study, one mutation in the IL1R1 gene, whose gene product increases inflammation, is connected to a greater level of stated cognitive function amongst breast cancer survivors. As a result of this discovery, a potential biomarker for identifying individuals undergoing chemotherapy who are less likely to develop cognitive dysfunction has been discovered. [55]

3. Targeting the depressive symptoms:
Sadness is one of the psychiatric problems connected to poor emotional, functional, physiological, and interpersonal well-being in breast cancer patients undergoing adjuvant cancer treatment. Other significant symptoms reported by women with breast cancer, such as pain, exhaustion, and sleep disruption, tend to form symptom clusters with it. [56] As a consequence, personalized antidepressant drugs may be a realistic option for improving breast cancer patients' quality of life. In a recent study, the gene encoding for neurologically neurotrophic factor was revealed to be a gene biomarker for depression, paving the way for an alternate method of identifying breast cancer patients who may be targeted for depression therapy, resulting in improved results. [57] [58]

Conclusion:
Precision medicine holds the promise of truly individualized therapy, for each breast cancer victim receiving the best diagnostics and targeted treatments based on the tumor's genetic profile, which is identified by a panel of gene tests and some other prognostic and predictive testing. Because of its huge promise and a slew of new possibilities, personalized medicine is gaining traction. A greatest objective of precision medicine is the discovery of individual genetic origins of illness. The incredible improvement of modern high-throughput technology, along with a better knowledge of the molecular mechanisms of cancer, has laid the groundwork for finding new molecular targets. Personalized medicine is routinely employed in BC treatment both in acute and metastatic settings, despite the fact that several parts of it are still under evaluation**.** It is possible to examine not just cancerous tissues, but also circulating tumor cells and DNA. Predictive or prediction genomic profiles are already used or being developed in local and metastatic illnesses to aid in therapeutic decisions. Several studies have looked at or are looking into therapy regimes in metastasis BC based on tumor genetic abnormalities revealed by array-CGH or next-generation sequencing methods.The fact, on the other hand, is that modern technology is now limited to grouping patients into smaller groups and administering precise targeted treatments to them. This approach, however, would then face various challenges and issues before ever being transcribed into the clinic, such as better accessibility to new genetic expeditions, this same emergence of future biostatistics, statistical data, and medical research techniques, and fresh perspectives about drug development due to the huge amount of cancer cell subgroups and systemic inflammation recognised by such tools. The notion of "single disease, single victim, one treatment" might lead to oncology's "El Dorado."

FINANCIAL SUPPORTS AND SPONSORSHIPS
Nil

CONFLICT OF INTEREST
None declared.

ACKNOWLEDGEMENT
The authors are incredibly thankful to Management, Dr. Vishwanath Karad MIT World Peace University,Pune for providing all necessary facilities in the publication of this paper. The authors are also thankful for various sources of the internet, google, and various newspapers, magazines for giving fruitful information for the publication of this paper.

CONTRIBUTION: Authors contributed equally from the conception, design, providing the study materials, and writing the manuscript.

References
1. Sagner M, and et.al . The P4 Health Spectrum - A Predictive, Preventive, Personalized and Participatory Continuum for Promoting Healthspan. Prog Cardiovasc Dis. 2017 Mar-Apr;59(5):506-521.
2. Pursel, Michael, et al. “Personalized medicine: part 1: evolution and development into theranostics, 2010 Oct;35(10):560-76.
3. Vogenberg FR, Barash CI, Pursel M. Personalized medicine: part 2: ethical, legal, and regulatory issues. P T. 2010 Nov;35(11):624-42.
4. Jakka, S., Rossbach, M. An economic perspective on personalized medicine, *HUGO J* , 2013,7(1) 1-6 https://doi.org/10.1186/1877-6566-7-1

5. Strasser, Kathrin. Identification of early breast cancer patient cohorts who may benefit from lapatinib therapy. Eur J Cancer. 2016 Mar; 56:85-92. doi: 10.1016/j.ejca.2015.12.024. Epub 2016 Jan 30.
6. Cameron, David. "11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet.389(10075) 2017 Mar 25;:1195-1205. doi: 10.1016/S0140-6736(16)32616-2.
7. Cullinane et.al Association of Circulating Tumor DNA With Disease-Free Survival in Breast Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Nov 2;3(11): e2026921. doi: 10.1001/jamanetworkopen.2020.26921.
8. Najafi et.al Randomized Study of the Effect of Dietary Counseling During Adjuvant Chemotherapy on Chemotherapy Induced Nausea and Vomiting, and Quality of Life in Patients With Breast Cancer. Nutr Cancer.71(4) 2019;:575-584. doi: 10.1080/01635581.2018.1527375. Epub 2018 Nov 17.
9. Wallerstedt, Susanna M. "Personalized medicine and the decision to withhold chemotherapy in early breast cancer with intermediate risk of recurrence - a systematic review and meta-analysis." 5 June 2020,.Eur J Clin Pharmacol. 2020 Sep;76(9):1199-1211. doi: 10.1007/s00228-020-02914-z. Epub 2020 Jun 5
10. Jiang, Yi Zhou. "Molecular subtyping and genomic profiling expand precision medicine in refractory metastatic triple-negative breast cancer: the FUTURE trial." 27 July 2020, 2021 Feb;31(2):178-186. doi: 10.1038/s41422-020-0375-9.
11. Sadée W, Dai Z. Pharmacogenetics/genomics and personalized medicine. Hum Mol Genet. 2005 Oct 15;14 Spec No. 2:R207-14. doi: 10.1093/hmg/ddi261.
12. Z, Tezak et.al . *US FDA and personalized medicine: in vitro diagnostic regulat*ory perspective. *Future Medicine, 517–530.* doi:10.2217/
13. Vu T, Claret FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. Front Oncol. 2012 Jun 18;2:62. doi: 10.3389/fonc.2012.00062.
14. Romero-Otero J et.al Active surveillance for prostate cancer. Int J Urol. 2016 Mar;23(3):211-8. doi: 10.1111/iju.13016. Epub 2015 Nov 30.
15. El Miedany Y. MABS: targeted therapy tailored to the patient's needs. Br J Nurs. 2015 Sep;24(16 Suppl 1):S4-13. doi: 10.12968/bjon.2015.24.sup16a.s4.
16. Mali P, Esvelt KM, Church GM. Cas9 as a versatile tool for engineering biology. Nat Methods. 2013 Oct;10(10):957-63. doi: 10.1038/nmeth.2649.
17. Cyranoski D. CRISPR gene-editing tested in a person for the first time. Nature. 2016 Nov 24;539(7630):479. doi: 10.1038/nature.2016.20988.
18. Collins, Francis S., and Harold Varmus. "A New Initiative on Precision Medicine." The New England Journal Of Medicine, 26 February 2015 793-795 doi:372910.1056/NEJMp150052325635347.
19. Yiwey Shieh et.al Breast Cancer Screening in the Precision Medicine Era: Risk-Based Screening in a Population-Based Trial, *JNCI: Journal of the National Cancer Institute*, Volume 109, Issue 5, May 2017, doi.org/10.1093/jnci/djw290
20. Chiu, Sherry.et.al "Cancer Epidemiology, Biomarkers & Prevention." American Association of Cancer Research 2010 19 (5): 1219–1228 doi.org/10.1158/1055-9965.EPI-09-1028
21. Engmann et.al Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer. *JAMA Oncol.* 2017;3(9):1228–1236. doi:10.1001/jamaoncol.2016.6326
22. Breast Cancer Surveillance Consortium. "Breast Cancer Surveillance Consortium Risk Calculator." 31 January 2016, https://tools.bcsc-scc.org/BC5yearRisk/intro.htm,
23. Boyd et.al Effects at Two Years of a Low-Fat, High-Carbohydrate Diet on Radiologic Features of the Breast: Results From a Randomized Trial, *JNCI: Journal of the National Cancer Institute*, Volume 89, Issue 7, 2 April 1997, Pages 488–496, . doi.org/10.1093/jnci89.7.488
24. Cigler *et al.* A randomized, placebo-controlled trial (NCIC CTG MAP.2) examining the effects of exemestane on mammographic breast density, bone density, markers of bone metabolism and serum lipid levels in postmenopausal women. *Breast Cancer Res Treat* 126, 453–461
25. Perou. *et al.* Molecular portraits of human breast tumors. *Nature* 406, 747–752 (2000).doi.org/10.1038/35021093
26. Prat, Aleix. et al.2010/09/02 Phenotypic and molecular characterization of the claudin-low

intrinsic subtype of breast cancer Breast Cancer Research doi.org/10.1186/bcr263527) Maisonneuve, P., Disalvatore, D., Rotmensz, N. *et al.* Proposed new clinicopathological surrogate definitions of luminal A and luminal B (HER2-negative) intrinsic breast cancer subtypes. *Breast Cancer Res* 16, R65 (2014). https://doi.org/10.1186/bcr3679

27. S, Therese. "Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications." 11 September 2001, https://www.pnas.org/doi/full/10.1073/pnas.191367098 .
28. K. David Voduc et.al "Breast Cancer Subtypes and the Risk of Local and Regional Relapse" Journal of Clinical Oncology 1684-1691 10.1200/JCO.2009.24.9284
29. vW, Pratyaksha. "Meta-analysis of gene expression profiles in breast cancer: toward a unified understanding of breast cancer subtyping and prognosis signatures - Breast Cancer Research." 28 July 2008 doi.org/10.1186/bcr2124
30. Paik, Soonmyung. "A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer." N Engl J Med 30 December 2004,; 351:2817-2826 DOI: 10.1056/NEJMoa041588
31. van de Vijver, Marc. "A Gene-Expression Signature as a Predictor of Survival in Breast Cancer."N Engl J Med 2002; 19 December 2009, 347:1999-2009 DOI: 10.1056/NEJMoa021967
32. Tian, Sun. "Biological Functions of the Genes in the Mammaprint Breast Cancer Profile Reflect the Hallmarks of Cancer." *Biomarker Insights*. Biological Functions of the Genes in the Mammaprint Breast Cancer Profile Reflect the Hallmarks of Cancer.January 2010. doi:10.4137/BMI.S6184
33. Parker, Joel S. "Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes." Journal of Clinical Oncology 2009 27:8, 1160-1167
34. Dowsett, Mitch. "Comparison of PAM50 Risk of Recurrence Score With Oncotype DX and IHC4 for Predicting Risk of Distant Recurrence After Endocrine Therapy." Journal of Clinical Oncology 2013 31:22, 2783-2790.
35. Harris, Lyndsay N. "Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline." Journal of Clinical Oncology 2016 34:10, 1134-1150
36. Badve, Sunil. "Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists." 12 November 2010.
37. Gaëlle Judes et.al High-throughput «Omics» technologies: New tools for the study of triple-negative breast cancer, Cancer Letters, Volume 382, Issue 1, 2016, Pages 77-85, https://doi.org/10.1016/j.canlet.2016.03.001.
38. Nanda, Rita. "Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2.", Journal of Clinical Oncology 2017 35:15_suppl, 506-506
39. Carel et.al Toward precision medicine of breast cancer. *Theor Biol Med Model* 13, 7 (2016 https://doi.org/10.1186/s12976-016-0035-4
40. Yu, Lin Yu. et.al New Immunotherapy Strategies in Breast Cancer. *Int. J. Environ. Res. Public Health* **2017**, *14*, 68. https://doi.org/10.3390/ijerph14010068
41. Bernstein, *et al.* Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach?. *Nat Rev Clin Oncol* 13, 516–524 (2016). https://doi.org/10.1038/nrclinonc.2016.30
42. BM Turner & DG Hicks (2017) Pathologic diagnosis of breast cancer patients: evolution of the traditional clinical-pathologic paradigm toward "precision" cancer therapy, Biotechnic & Histochemistry, 92:3, 175-200, DOI: 10.1080/10520295.2017.1290276
43. Rahbar, Habib. "How Can Advanced Imaging Be Used to Mitigate Potential Breast Cancer Overdiagnosis?" 1 June 2016, https://www.academicradiology.org/article/S1076-6332(16)00108-2/fulltext . Accessed 10 July 2022.
44. Khul, Christiane K. "MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study.", Lancet 2007; 370: 11 August 2007 485–92, https://doi.org/10.1016/S0140-6736(07)61232-X
45. Li, Hui. "Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA data set." 11 May 2016, https://www.nature.com/articles/npjbcancer201612 . Accessed 10 July 2022.
46. Blaschke, Eric. "MRI phenotype of breast cancer: Kinetic assessment for molecular subtypes." 9 March 2015,

https://onlinelibrary.wiley.com/doi/10.1002/jmri.24884 .
47. Yamaguchi, Ken et.al. Intratumoral heterogeneity of the distribution of kinetic parameters in breast cancer: comparison based on the molecular subtypes of invasive breast cancer. *Breast Cancer* 22, 496–502 (2015). https://doi.org/10.1007/s12282-013-0512-0
48. Osborne CK, McGuire WL. The use of steroïd hormone receptors in the treatment of human breast cancer: a review. Bull Cancer. 1979;66(3):203-9.
49. Heuson JC et.al Significance of quantitative assessment of estrogen receptors for endocrine therapy in advanced breast cancer. Cancer. 1977 May;39(5):1971-7. doi: 10.1002/1097-0142(197705)39:5<1971::aid-cncr2820390510>3.0.co;2-8.
50. Winters, Kerri M. "Comparison of physical function and falls among women with persistent symptoms of chemotherapy-induced peripheral neuropathy."Journal of Clinical Oncology 2016 34:3_suppl, 130-130
51. Winters-Stone et.al Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. J Clin Oncol. 2017 Aug 10;35(23):2604-2612. doi: 10.1200/JCO.2016.71.3552. Epub 2017 Jun 6.
52. Loh, et.al Chemotherapy-related cognitive impairment in older patients with cancer. J Geriatr Oncol. 2016 Jul;7(4):270-80. doi: 10.1016/j.jgo.2016.04.008. Epub 2016 Jul 5.
53. Myers et.al Perceived cognitive function for breast cancer survivors: association of genetic and behaviorally related variables for inflammation. Support Care Cancer. 2017 Aug;25(8):2475-2484. doi: 10.1007/s00520-017-3654-3. Epub 2017 Mar 1.
54. Fiorentino et.al The Symptom Cluster of Sleep, Fatigue and Depressive Symptoms in Breast Cancer Patients: Severity of the Problem and Treatment Options. Drug Discov Today Dis Models. 2011 Winter;8(4):167-173. doi: 10.1016/j.ddmod.2011.05.001.
55. Strasser, Kathrin. Et.al Identification of early breast cancer patient cohorts who may benefit from lapatinib therapy. Eur J Cancer. 2016 Mar; 56:85-92. doi: 10.1016/j.ejca.2015.12.024. Epub 2016 Jan 30.
56. Cameron et.al 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017 Mar 25;389(10075):1195-1205. doi: 10.1016/S0140-6736(16)32616-2. Epub 2017 Feb 17. Erratum in: Lancet. 2019 Mar 16;393(10176):1100.
57. Cullinane et.al Association of Circulating Tumor DNA With Disease-Free Survival in Breast Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Nov 2;3(11):e2026921. doi: 10.1001/jamanetworkopen.2020.26921.