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Pharmacogenomics: Personalized medicine and its impact on breast cancer

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***Abstract*---**Background: Personalized medicine in breast cancer aims to optimize treatment by classifying cancer subtypes and tailoring therapy based on individual patient profiles, including genetic and epigenetic factors. Pharmacogenomics plays a crucial role in this strategy by investigating how genetic variations affect drug metabolism and therapy response. Aim: This article reviews the impact of pharmacogenomics on personalized medicine for breast cancer, focusing on different molecular subtypes and their responses to targeted therapies. Methods: The study involved a comprehensive review of current literature, examining the molecular classification of breast cancer, the role of genetic and epigenetic factors, and advancements in pharmacogenomics. Key resources, including open-source databases and clinical trials, were analyzed to understand treatment resistance and efficacy. Results: Breast cancer is categorized into molecular subtypes such as hormone receptor-positive, HER2-positive, and triple-negative. Each subtype exhibits distinct responses to therapies. For instance, hormone receptor-positive cancers benefit from endocrine therapies, while HER2-positive cancers respond to targeted antibodies. Triple-negative breast cancer, characterized by its heterogeneity, shows varied responses to platinum-based compounds and PARP inhibitors. The study highlights the challenges of drug resistance and the potential of personalized therapies to overcome these issues. Conclusion: Pharmacogenomics significantly enhances personalized medicine for breast cancer by enabling tailored treatments based on genetic profiles. Despite progress, challenges such as drug resistance and tumor heterogeneity remain. Future advancements in genetic and genomic understanding, along with the integration of personalized strategies, are crucial for improving treatment outcomes.

***Keywords*---**pharmacogenomics, breast cancer, personalized medicine, drug resistance, molecular subtypes, targeted therapies.

Introduction

Providing optimal treatment in personalized medicine for breast cancer is critically important. This strategy facilitates the classification of cancer subtypes, thereby enabling the selection of the most appropriate treatment regimen based on patient-specific factors, including medical history and therapy response [1][2]. Pharmacological strategies, such as pharmacogenetics and pharmacodynamics, are instrumental in tailoring therapeutic decisions. These approaches assist clinicians in choosing suitable drugs and dosages to minimize adverse effects and enhance treatment efficacy. The systematic investigation of drug absorption, distribution, and metabolism, influenced by genetic and epigenetic variations, is vital for therapeutic success [3]. Alongside genetic polymorphisms, epigenetic factors, microbiome changes, and demographic attributes contribute to multi-drug resistance [4–6]. Historically, pharmacogenetics and pharmacogenomics examine the impact of genetic variations on drug metabolism and the overall genomic response to medications [7]. These methodologies are increasingly utilized in oncology to mitigate toxicity while optimizing the effectiveness of targeted therapies and chemotherapy. They are also pivotal in drug development, leveraging genetic profiling and innovative techniques.

Molecular Classification

Breast cancer is categorized into five molecular classes based on molecular stratification: 1) hormone receptor-positive (luminal A and luminal B), 2) HER2-positive, 3) basal-like, 4) normal-like, and 5) claudin-low, which corresponds to triple-negative breast cancer (TNBC) with medullary and metaplastic differentiation [8][9][10][11][12][13]. Each molecular subtype demonstrates distinct treatment responses [9][10]. The luminal A subtype, which constitutes 40%-60% of cases and is predominantly ER+/PR+ and HER2-negative, exhibits a low pathological grade and proliferation rate, showing minimal response to chemotherapy but sensitivity to endocrine therapy [8][14][15][16][17]. Luminal B (ER+/PR+ and HER2-positive) represents 15% of cases, with higher pathological grades and proliferation rates, benefiting more from chemotherapy than anti-estrogen drugs [14][15][18]. HER2-positive tumors, making up 10% of cases, present a high pathological grade and, although chemosensitive, had poor prognoses until targeted therapies emerged [14][15][19][20][21]. Basal-like tumors, accounting for 10–25% of cases, overlap with TNBC and exhibit aggressive behavior and poor prognosis, though they are chemosensitive [13][19][22–24]. The normal-like subtype, comprising 3–10% of cases, shows intermediate prognosis, with some studies suggesting that these may be technical artifacts [12][25]. Claudin-low tumors, predominantly TNBC and constituting 7–14% of cases, show reduced expression of claudin and E-cadherin genes, with 15% expressing ER and 15% overexpressing HER2 [12][26]. These tumors exhibit an intermediate response to chemotherapy [12][13]. Despite significant advancements in therapeutic strategies for breast cancer, challenges such as both de novo and acquired resistance remain. A thorough understanding of the molecular mechanisms underlying different breast cancer subgroups is essential for developing more effective treatment approaches. Targeting specific molecules or mutated genes offers promising potential for personalized therapies. Enhanced insights into these mechanisms can drive innovative drug development and

therapeutic strategies, potentially overcoming current limitations and improving patient outcomes. As personalized medicine evolves, integrating molecular knowledge into clinical practice will be critical in addressing the complexities of breast cancer treatment and resistance.

Heterogeneity Resources

The heterogeneity observed in breast cancer subtypes is a leading cause of therapeutic failure and unpredictable outcomes. Variations in genetic and epigenetic features within a subset of cancer cells can alter prognosis and drug responsiveness [5][29]. This heterogeneity can be categorized as intra-tumoral—where it affects cells within a single tumor—or inter-tumoral, affecting cells from the same cancer subtype across different patients. Intra-tumor heterogeneity may be "spatial," affecting specific regions of the tumor, or "temporal," involving changes in cells over time, from the primary tumor to metastatic sites. Heterogeneity at the morphological level is assessed through histopathological comparisons and grading systems [30]. At the genetic level, variations include copy number alterations (CNVs), gene overexpression or down-regulation, and mutations such as missense, nonsense, and frameshift [5]. Open-source databases like COSMIC and TCGA provide comprehensive data on high-throughput techniques and genetic variations. These databases categorize heterogeneity into local and systemic sources [5]. The COSMIC database offers extensive information from numerous breast cancer tumors analyzed across different platforms, detailing various analyses, mutations, CNVs, and expression levels. This variability, whether spatial or temporal, contributes to diverse tumor responses to treatment regimens.

The pharmacogenomics approach identifies genetic variations in driver genes that promote selective tumor growth. This information aids clinicians in choosing effective therapeutic regimens to counteract resistance. Considerations include selecting appropriate drug combinations and targeting subclonal populations that may develop adaptive responses or experience toxicity [3]. Accurate detection of subclonal populations, such as through ex vivo tumor culture methods, remains a critical challenge [31][32]. Passenger mutations, present in genes that support tumor survival, are acquired during normal cell states or after neoplastic transformation [5]. Additionally, genes associated with cancer development may not always be mutated but can be inactivated through epigenetic mechanisms.

Hereditary breast cancer is linked to genetic mutations in genes such as BRCA1, BRCA2, PALB2, TP53, CDH1, and PTEN, which are associated with increased breast cancer risk [33]. Epigenetic mechanisms also play a significant role, as evidenced by the frequent hypermethylation and silencing of the tumor suppressor gene RASSF1A in breast cancer [34]. Familial breast cancer is often attributed to mutations in BRCA1 and BRCA2, while sporadic cases show a 10–15% rate of BRCA1 methylation. Key molecular pathways involved in breast cancer progression include the PI3K/AKT/mTOR and RAS/RAF/MEK pathways, which are frequently aberrantly activated and linked to drug resistance [35]. Clinical trials are exploring PI3K inhibitors targeting these pathways, and PTEN inactivation by epigenetic mechanisms may extend the use of effective inhibitors

for PTEN-deficient cancers. Additionally, PPP2R2B, a negative regulator of AKT, is often subject to promoter methylation in breast cancer [36].

In gene families, mutations and methylation overlaps can lead to variable responses, as exemplified by RUNX1 mutations and RUNX3 inactivation through epigenetic mechanisms [15][37]. DNA methylation analysis in blood samples using bisulfite-based PCR techniques is a powerful tool for investigating these variations [15]. Tumor heterogeneity is further influenced by the tumor microenvironment, including tumor-associated macrophages, fibroblasts, bone marrow-derived cells, lymphatic growth factors, chemokines, cytokines, and exosomes, which contribute to tumor growth and metastasis [5]. Future advancements in genetic, genomic, and immunologic consultation are anticipated to guide oncologists in devising tailored treatment strategies. Pharmacogenomics will play a crucial role in the development of personalized therapies, enhancing treatment efficacy and overcoming resistance challenges.

Pharmacogenetics in Breast Cancer Subtypes
Estrogen Receptor Positive (ER+) Subtype

Estrogen receptor-positive (ER+) breast cancer is the most prevalent subtype and is characterized by the expression of estrogen receptors, which serve as a predictive marker for patient monitoring and disease-free status [38][39]. This subtype typically benefits from hormonal therapies, such as the synthetic estrogen analog tamoxifen (TAM). TAM binds to the estrogen receptor and disrupts the classical signaling pathway that promotes ductal hyperplasia, thereby altering the tumor microenvironment and affecting the invasive state of the cancer [38][39]. ER overexpression also engages non-classical functions that affect genomic activity independently of hormones, through growth factor signaling pathways like FGFR, IGFR, and GPCRs, which activate intracellular kinases and phosphatases. Research has demonstrated that kinases influence ER phosphorylation, which correlates with either sensitivity or resistance to endocrine therapies [40]. Baron et al. have reviewed phosphorylation sites and mRNA splicing regions in ER, linking these to drug responses.

The interaction between ER and other transcription factors, such as C-Fos/C-Jun (AP-1), Sp1, and NF-KB, contributes to tumor cell proliferation, angiogenesis, and metastasis [40]. In addition to TAM, Fulvestrant, an ER down-regulator, has been approved for ER+ breast cancer treatment. Fulvestrant binds to ER, preventing its dimerization and promoting its degradation. Aromatase inhibitors like Anastrozole, which block estrogen conversion from adrenal androgens, are also used, particularly in postmenopausal women [39]. TAM's efficacy is consistent regardless of menopausal status. Variations in hormone receptor subtypes, such as progesterone receptor (PR) expression, influence treatment outcomes. ER+ tumors that also express PR generally have a better prognosis, while PR-negative tumors, which do not respond as well to TAM, benefit from Anastrozole [41].

Primary endocrine resistance occurs in approximately 50% of ER+ cases, with an additional 50% developing acquired resistance over time. Factors contributing to resistance include mutation rates, methylation, acetylation, downregulation of ERα, overexpression of ERβ, and interactions between ER and growth factor

signaling pathways [40][42]. ARN-810, a selective ERα antagonist, targets ESR1 mutations, providing efficacy where traditional endocrine therapies fall short [43]. ESR1 mutations in the ligand-binding domain (e.g., Y537S, Y537N, Y537C, and D538G) are linked to ligand-independent transcriptional activity and are a major resistance mechanism in recurrent and metastatic cancer [44][46]. These mutations, though rare in primary tumors, are prevalent in over 20% of cases with recurrence and are more common in metastatic cancer compared to primary cases. Detection of ESR1 mutations in plasma cfDNA can guide treatment strategies, with Fulvestrant showing improved tumor-free survival in ESR1-mutant cases [48][49]. The combination of Fulvestrant with Palbociclib has been beneficial for metastatic cancer patients with ER mutations [50]. The COSMIC database reports that ESR1 mutation Y537S affects IGF1R phosphorylation, correlating with shorter overall survival and resistance to targeted therapies [51][42]. Other mutations, such as K303R, reduce TAM sensitivity through AKT phosphorylation [52]. Additionally, PIK3CA mutations are common in ER+ cases, with the Luminal B subtype showing moderate PTEN reduction and enhanced PI3K signaling. Combination therapies involving mTOR, AKT, or MEK inhibitors with Fulvestrant improve outcomes, as Luminal B tumors are more aggressive and resistant compared to Luminal A [53][54].

Pharmacogenetics plays a crucial role in the management of ER+ breast cancer by identifying genetic variations that influence drug responses and resistance mechanisms. The variability in ER+ breast cancer subtypes necessitates tailored therapeutic approaches to address primary and acquired resistance. Advanced therapies, such as Fulvestrant and PI3K inhibitors, combined with targeted strategies for specific mutations, represent promising advancements in overcoming resistance. Despite significant progress, challenges remain in predicting and managing resistance, emphasizing the need for continued research into biomarkers and personalized treatments. The integration of pharmacogenomics into clinical practice holds the potential to enhance treatment efficacy and patient outcomes, particularly for those with resistant or advanced disease. Addressing drug resistance remains a critical focus to improve long-term survival and quality of life for ER+ breast cancer patients.

HER2 Positive Breast Cancer
HER2 Amplification and Resistance

HER2-positive breast cancer, characterized by the overexpression of the HER2 receptor, accounts for over 14% of metastatic cases. This amplification is linked to increased cell proliferation, angiogenesis, invasion, and reduced apoptosis [64]. In HER2-negative tumors, compensatory oncogenes such as BRF2 and DSN1 may be amplified or overexpressed, providing a neoplastic advantage [29].

HER2+ patients respond well to targeted therapies, including HER2 antibodies and kinase inhibitors such as lapatinib, pertuzumab, trastuzumab, ado-trastuzumab, and emtansine [65]. Trastuzumab (Herceptin™) was the first humanized monoclonal antibody developed against HER2 and received FDA approval as a targeted therapy for breast cancer [66][67]. Clinical studies have shown that combining trastuzumab with standard chemotherapy often results in better outcomes than chemotherapy alone [68][70]. However, resistance to

trastuzumab can develop, predominantly due to mechanisms related to HER2 signaling pathways, and is associated with mutations in PIK3CA, RAS, Src, NF-KB, and inactivating mutations in PTEN [71][75].

Resistance to trastuzumab can also occur due to truncated isoforms of HER2 that lack the trastuzumab target epitope, resulting in stable HER2 homodimers [76][77][78]. Additionally, overexpression of EGFR and HER-3, and their interactions with adhesion molecules like MUC1-C or MUC4, contribute to resistance [73][80]. Strategies to overcome resistance include:

1. PI3K and mTOR Pathway Inhibitors: Pan PI3K inhibitors, specific PIK3CA inhibitors, AKT inhibitors, and mTOR inhibitors can address resistance due to PIK3CA alterations.
2. Lapatinib: Combines with trastuzumab to overcome high levels of p95HER2.
3. Tyrosine Kinase Inhibitors: Target IGF1R tyrosine kinase receptor.
4. MET Inhibitors: Address MET alterations.
5. Immune Checkpoint Inhibitors: Target low immune responses [81].

Trastuzumab-DM1 (T-DM1), a novel monoclonal antibody conjugated with maytansine, requires high HER2 expression for efficacy. Low intra-tumor HER2 levels and poor internalization of the HER2-drug can lead to resistance [83][84]. CYD985, another antibody-drug conjugate, has shown promise in T-DM1-pretreated patients [85]. Lapatinib inhibits EGFR and HER2 autophosphorylation, and its combination with trastuzumab targets both intracellular and extracellular HER2 domains [86][88]. However, resistance to lapatinib can occur due to HER2 overexpression and AXL activation [89][90]. Pertuzumab, which binds to a different HER2 extracellular domain than trastuzumab, inhibits HER2 dimerization and can partially reverse trastuzumab resistance [91][92]. Combining pertuzumab with lapatinib has shown effectiveness in overcoming resistance [93]. Ertumaxomab, still under clinical evaluation, might offer additional targeted therapy options [93]. Neratinib, a reversible tyrosine kinase inhibitor, has demonstrated improved disease-free survival in patients with recurrent and metastatic tumors [94][96]. Afatinib, another kinase inhibitor, has been effective in both preclinical and clinical studies, showing longer effects compared to other EGFR inhibitors [97][98][99].

Triple-Negative Breast Cancer (TNBC)

Triple-negative breast cancer (TNBC) encompasses three subtypes: normal-like, basal-like, and non-basal-like. About 75% of basal-like cancers are triple-negative, and 80% of these cases exhibit TP53 mutations (nonsense and frameshift) [100]. Basal-like and non-basal TN cancers show distinct mutations related to homologous recombination deficiency (HRD) and repair (HRR). Homologous recombination is crucial for repairing double-strand DNA breaks (DSBs), and clinical trials have highlighted HRD as a predictor of therapeutic response [100][102].

COSMIC database analysis identifies several genes involved in TNBC variations, including TP53, BRCA1, PIK3CA, RB, and PTEN. In TN tumors, TP53 and BRCA1 mutations do not correlate, though BRCA1 methylation has been associated with

TP53 mutations [103][104]. Increased PIK3CA mutations, loss of PTEN and INPP4B, and EGFR overexpression activate the PI3K pathway. In basal-like tumors, 72% are RB-/P16+ with high p53 expression, correlating with high proliferation. Mutations in BRCA1, PTEN, and ERBB2 are linked to a higher risk of metastasis [100].

Platinum-based compounds, which induce DSBs, are relevant for treating cells with defective DNA repair mechanisms. PARP inhibitors are effective in cancers with defective DSB repair by blocking PARP1 activity, leading to accumulation of unrepaired single-strand breaks and DSBs, particularly in BRCA1 or BRCA2 defective cells [15]. While PARP inhibitors showed initial promise in TNBC, subsequent trials have not consistently confirmed these results, making it unclear which subsets of TNBC or inherited BRCA mutations benefit from these treatments [106][107]. Platinum-based agents, such as cisplatin, target lesions that are ineffectively repaired due to DSB formation, but mutations in TP53 can lead to cisplatin resistance [108]. Targeted therapies combined with chemotherapy may overcome PI3K/AKT/mTOR pathway mutations in TNBC [5].

Chemotherapy in Breast Cancer Treatment

Chemotherapy remains a cornerstone in the treatment of both primary and metastatic breast cancer, utilizing a range of systemic medications to target and eliminate cancer cells [108]. Several classes of chemotherapy drugs are used, each with distinct mechanisms and challenges:

1. Anthracyclines: This class includes doxorubicin, epirubicin, and mitoxantrone. Anthracyclines are known for their pleiotropic effects, inducing cell death through various mechanisms [109][110][112]. Resistance to anthracyclines often arises from increased expression of P-glycoprotein, leading to drug efflux [113]. Strategies to overcome resistance include the use of novel topoisomerase II inhibitors like fostriecin and merbarone, non-cross-resistant drugs, and modifications in drug delivery [114][119].
2. Taxanes: Paclitaxel, docetaxel, and nab-paclitaxel are taxanes that bind to microtubules, inhibiting mitosis and disrupting cell division [120]. Resistance mechanisms include alterations in beta-tubulin expression and upregulation of caveolin-1. Overcoming resistance involves using agents like cyclosporine A, PC833, and verapamil, as well as new microtubule inhibitors like ixabepilone and eribulin [121][123].
3. Antimetabolites: Drugs such as methotrexate (MTX) and 5-fluorouracil (5-FU) target specific enzymes involved in DNA synthesis. Resistance to MTX can result from decreased drug uptake, increased efflux, and reduced polyglutamation [126][134]. 5-FU resistance is often due to alterations in its metabolism [135]. Strategies to overcome resistance include manipulating drug metabolism, using high doses, and developing new antimetabolites [136].
4. Alkylating Agents and Platinum-based Drugs: These drugs alkylate DNA, forming reactive intermediates that interfere with DNA repair [109]. Tumors may develop resistance through decreased drug accumulation, increased drug inactivation, and enhanced DNA repair mechanisms [137][139]. Vinca

alkaloids (e.g., vincristine, vinblastine) also face multidrug resistance due to decreased drug accumulation, with potential solutions including DNA polymerase alpha inhibitors like gemcitabine [141][142].

New Challenges in Precision Medicine

Despite advances, significant challenges remain in precision medicine:

1. Drug Safety and Efficacy: The development of safe and effective drugs is critical. For instance, metformin, an antihyperglycemic drug, has shown potential in reducing cancer rates, including breast cancer [143]. It inhibits cancer cell proliferation and invasion, potentially through its effects on tumor suppressor microRNA miR-200c [144]. Understanding the molecular mechanisms of metformin and developing advanced generations of the drug could improve therapeutic outcomes [145].
2. Personalized Medicine Factors: Personalized approaches must consider factors like diet, psycho-social status, and hormonal influences. Vitamin D, which affects nearly all cells, plays a role in breast cancer prevention [146]. Epidemiological studies suggest that vitamin D and related genes impact disease risk. Psycho-social factors such as stress, depression, and anxiety also significantly influence breast cancer development and treatment response [147][149]. Dopamine and serotonin have emerged as potential targets, with studies showing changes in receptor gene expression related to spiritual interventions and serotonin levels [150][151].
3. Microbiome Profiling: The role of the microbiome in breast cancer etiology is gaining attention. Differences in bacterial profiles between tumor-adjacent tissues and healthy controls may provide insights into disease mechanisms [152].
4. Systems Biology: Modern diagnostics and therapeutics leverage systems biology, which integrates data from various sources to understand complex biological interactions. This approach aids in developing personalized treatments by analyzing interactions between cellular components and identifying novel biomarkers and therapeutic targets [153-155].

Overall, integrating these advancements into clinical practice will enhance the precision of breast cancer treatment and improve patient outcomes.

Conclusion

Pharmacogenomics has transformed the landscape of personalized medicine in breast cancer by enabling the development of targeted treatments based on individual genetic profiles. This approach has been instrumental in improving the efficacy of therapies and reducing adverse effects. Breast cancer's classification into molecular subtypes—such as hormone receptor-positive (ER+), HER2-positive, and triple-negative—has facilitated a more precise application of treatments. Each subtype demonstrates distinct molecular characteristics and therapeutic responses, which are critical for designing effective treatment strategies. The integration of pharmacogenomics into clinical practice addresses the complexities of breast cancer, particularly in overcoming drug resistance and managing tumor heterogeneity. For ER+ breast cancer, targeted therapies like

tamoxifen and aromatase inhibitors have been beneficial, though resistance remains a significant challenge due to mutations and variations in hormone receptor expression. HER2-positive breast cancer has seen substantial improvements with targeted therapies like trastuzumab, but resistance due to mutations and alterations in signaling pathways continues to pose challenges. In triple-negative breast cancer (TNBC), the variability in responses to treatments such as platinum-based drugs and PARP inhibitors highlights the need for ongoing research and development. Despite these advancements, several challenges persist. Drug resistance, due to both genetic and epigenetic factors, and the intrinsic heterogeneity of tumors complicate treatment outcomes. The role of pharmacogenomics in addressing these issues is vital for developing more effective personalized therapies. Future research should focus on improving our understanding of tumor biology, enhancing the accuracy of genetic profiling, and integrating these insights into clinical practice. Overall, pharmacogenomics holds promise for advancing personalized medicine in breast cancer, offering hope for better-targeted treatments and improved patient outcomes. Continued innovation in genetic research and therapeutic strategies will be essential in addressing current limitations and achieving more precise and effective cancer care.

References

1. Wang C, Machiraju R, Huang K. Breast cancer patient stratification using a molecular regularized consensus clustering method. *Methods*. 2014;67(3):304–312. doi:10.1016/j.ymeth.2014.03.00524657666
2. Chen X, Shachter RD, Kurian AW, Rubin DL. Dynamic strategy for personalized medicine: an application to metastatic breast cancer. *J Biomed Inform*. 2017;68:50–57. doi:10.1016/j.jbi.2017.02.01228232241
3. Nerenz RD. Pharmacogenomics and personalized medicine in the treatment of human diseases. In: Coleman WB, Tsongalis GJ, editors. *Molecular pathology*. 2nd ed. Elsevier; New York: Chapel Hill; 2018;731–743.
4. Li H, Jia W. Cometabolism of microbes and host: implications for drug metabolism and drug-induced toxicity. *Clin Pharmacol Ther*. 2013;94(5):574–581. doi:10.1038/clpt.2013.15723933971
5. Nandy A, Gangopadhyay S, Mukhopadhyay A. Individualizing breast cancer treatment—the dawn of personalized medicine. *Exp Cell Res*. 2014;320(1):1–11. doi:10.1016/j.yexcr.2013.09.00224051330
6. Alomar MJ. Factors affecting the development of adverse drug reactions. *Saudi Pharm J*. 2014;22(2):83–94. doi:10.1016/j.jsps.2013.02.00324648818
7. Dickmann LJ, Ware JA. Pharmacogenomics in the age of personalized medicine. *Drug Discov Today Technol*. 2016;21:11–16. doi:10.1016/j.ddtec.2016.11.00327978982
8. Eroles P, Bosch A, Pérez-Fidalgo JA, Lluch A. Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. *Cancer Treat Rev*. 2012;38(6):698–707. doi:10.1016/j.ctrv.2011.11.00522178455
9. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747. doi:10.1038/3502055710963602
10. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc*

Natl Acad Sci. 2001;98(19):10869–10874. doi:10.1073/pnas.19136709811553815

11. Herschkowitz JI, Simin K, Weigman VJ, et al. Identification of conserved gene expression features between murine mammary carcinoma models and human breast tumors. *Genome Biol*. 2007;8(5):R76. doi:10.1186/gb-2007-8-5-r8117493263
12. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. *Mol Oncol*. 2011;5(1):5–23. doi:10.1016/j.molonc.2010.11.00321147047
13. Perou CM. Molecular stratification of triple-negative breast cancers. *Oncologist*. 2011;16(Supplement 1):61–70. doi:10.1634/theoncologist.2011-S1-61
14. Sørlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc National Acad Sci*. 2003;100(14):8418–8423. doi:10.1073/pnas.0932692100
15. Stefansson OA, Esteller M. Epigenetic modifications in breast cancer and their role in personalized medicine. *Am J Pathol*. 2013;183(4):1052–1063. doi:10.1016/j.ajpath.2013.04.03323899662
16. Gnant M, Harbeck N, St. Gallen TC. summary of the consensus discussion. *Breast Care*. 2011;6(2
17. Del Mastro L, De Placido S, Bruzzi P, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2×2 factorial, randomised phase 3 trial. *Lancet*. 2015;385(9980):1863–1872. doi:10.1016/S0140-6736(14)62048-125740286
18. Creighton CJ. The molecular profile of luminal B breast cancer. *Biologics*. 2012;6:289.22956860
19. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res*. 2005;11(16):5678–5685. doi:10.1158/1078-0432.CCR-04-242116115903
20. Network CGA. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490(7418):61. doi:10.1038/nature1141223000897
21. Colozza M, de Azambuja E, Cardoso F, Bernard C, Piccart MJ. Breast cancer: achievements in adjuvant systemic therapies in the pre-genomic era. *Oncologist*. 2006;11(2):111–125. doi:10.1634/theoncologist.11-2-11116476832
22. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the carolina breast cancer study. *JAMA*. 2006;295(21):2492–2502. doi:10.1001/jama.295.21.249216757721
23. Rakha EA, El-Rehim DA, Paish C, et al. Basal phenotype identifies a poor prognostic subgroup of breast cancer of clinical importance. *Eur J Cancer*. 2006;42(18):3149–3156. doi:10.1016/j.ejca.2006.08.01517055256
24. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res*. 2004;10(16):5367–5374. doi:10.1158/1078-0432.CCR-04-022015328174
25. Weigelt B, Mackay A, A'Hern R, et al. Breast cancer molecular profiling with single sample predictors: a retrospective analysis. *Lancet Oncol*. 2010;11(4):339–349.

26. Prat A, Parker JS, Karginova O, et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. *Breast Cancer Res*. 2010;12(5):R68. doi:10.1186/bcr272220813035
27. Cadoo KA, Traina TA, King TA. Advances in molecular and clinical subtyping of breast cancer and their implications for therapy. *Surg Oncol Clin*. 2013;22(4):823–840. doi:10.1016/j.soc.2013.06.006
28. Fang L, Barekati Z, Zhang B, Liu Z, Zhong X. Targeted therapy in breast cancer: what's new. *Swiss Med Wkly*. 2011;141:w13231.21706452
29. Ng CK, Martelotto LG, Gauthier A, et al. Intra-tumor genetic heterogeneity and alternative driver genetic alterations in breast cancers with heterogeneous HER2 gene amplification. *Genome Biol*. 2015;16(1):107. doi:10.1186/s13059-015-0667-425994018
30. Zardavas D, Irrthum A, Swanton C, Piccart M. Clinical management of breast cancer heterogeneity. *Nat Rev Clin Oncol*. 2015;12(7):381. doi:10.1038/nrclinonc.2015.7325895611
31. Tsai H-F, Trubelja A, Shen AQ, Bao G. Tumour-on-a-chip: microfluidic models of tumour morphology, growth and microenvironment. *J R Soc Interface*. 2017;14(131):20170137. doi:10.1098/rsif.2017.013728637915
32. Ahn J, Sei Y, Jeon N, Kim Y. Tumor microenvironment on a chip: the progress and future perspective. *Bioengineering*. 2017;4(3):64. doi:10.3390/bioengineering4020044
33. Peters ML, Garber JE, Tung N. Managing hereditary breast cancer risk in women with and without ovarian cancer. *Gynecol Oncol*. 2017;146(1):205–214. doi:10.1016/j.ygyno.2017.04.01328454658
34. Kristiansen S, Nielsen D, Sölétormos G. Detection and monitoring of hypermethylated RASSF1A in serum from patients with metastatic breast cancer. *Clin Epigen*. 2016;8(1):35. doi:10.1186/s13148-016-0199-0
35. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res*. 2000;28(1):27–30.10592173
36. Sangodkar J, Farrington CC, McClinch K, Galsky MD, Kastrinsky DB, Narla G. All roads lead to PP 2A: exploiting the therapeutic potential of this phosphatase. *FEBS J*. 2016;283(6):1004–1024. doi:10.1111/febs.1357326507691
37. Lau QC, Raja E, Salto-Tellez M, et al. RUNX3 is frequently inactivated by dual mechanisms of protein mislocalization and promoter hypermethylation in breast cancer. *Cancer Res*. 2006;66(13):6512–6520. doi:10.1158/0008-5472.CAN-06-036916818622
38. Pietras RJ, Márquez-Garbán DC. Membrane-associated estrogen receptor signaling pathways in human cancers. *Clin Cancer Res*. 2007;13(16):4672–4676. doi:10.1158/1078-0432.CCR-07-137317699844
39. Russell CA. Personalized medicine for breast cancer: it is a new day! *Am J Surg*. 2014;207(3):321–325. doi:10.1016/j.amjsurg.2013.10.01624581758
40. Barone I, Brusco L, Fuqua SA. Estrogen receptor mutations and changes in downstream gene expression and signaling. *Clin Cancer Res*. 2010;15;16(10):1078–1432. CCR-09-1753.
41. De Abreu FB, Wells WA, Tsongalis GJ. The emerging role of the molecular diagnostics laboratory in breast cancer personalized medicine. *Am J Pathol*. 2013;183(4):1075–1083. doi:10.1016/j.ajpath.2013.07.00223920325
42. Yanagawa T, Kagara N, Miyake T, et al. Detection of ESR1 mutations in plasma and tumors from metastatic breast cancer patients using next-

generation sequencing. *Breast Cancer Res Treat*. 2017;163(2):231–240. doi:10.1007/s10549-017-4190-z28283903

43. Mayer IA. Advanced hormone-sensitive breast cancer: overcoming resistance. *J Natl Compr Canc Netw*. 2015;13(5S):655–657.25995422
44. Downey C, Simpkins S, White J, et al. The prognostic significance of tumour–stroma ratio in oestrogen receptor-positive breast cancer. *Br J Cancer*. 2014;110(7):1744. doi:10.1038/bjc.2014.6924548861
45. Takeshita T, Yamamoto Y, Yamamoto-Ibusuki M, et al. Clinical significance of monitoring ESR1 mutations in circulating cell-free DNA in estrogen receptor positive breast cancer patients. *Oncotarget*. 2016;7(22):32504. doi:10.18632/oncotarget.883927102299
46. Tabarestani S, Motallebi M, Akbari ME. Are estrogen receptor genomic aberrations predictive of hormone therapy response in breast cancer? *Iran J Cancer Prev*. 2016;9:4. doi:10.17795/ijcp
47. Segal CV, Dowsett M. Estrogen receptor mutations in breast cancer—new focus on an old target. *Clin Cancer Res*. 2014;20(7):1724–1726. doi:10.1158/1078-0432.CCR-14-006724583794
48. Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 mutations and the treatment of estrogen receptor-positive advanced breast cancer. J Clin Oncol. 2016;34:2961–2968.
49. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17(4):425–439. doi:10.1016/S1470-2045(15)00613-026947331
50. Lauring J, Wolff AC. Evolving role of the estrogen receptor as a predictive biomarker: ESR1 mutational status and endocrine resistance in breast cancer. *J Clin Oncol*. 2016;34(25):2950–2952. doi:10.1200/JCO.2016.68.472027382095
51. Gelsomino L, Gu G, Rechoum Y, et al. ESR1 mutations affect anti-proliferative responses to tamoxifen through enhanced cross-talk with IGF signaling. *Breast Cancer Res Treat*. 2016;157(2):253–265. doi:10.1007/
52. Fuqua SA, Gu G, Rechoum Y. Estrogen receptor (ER) α mutations in breast cancer: hidden in plain sight. *Breast Cancer Res Treat*. 2014;144(1):11–19. doi:10.1007/s10549-014-2847-424487689
53. Fu X, Creighton CJ, Biswal NC, et al. Overcoming endocrine resistance due to reduced PTEN levels in estrogen receptor-positive breast cancer by co-targeting mammalian target of rapamycin, protein kinase B, or mitogen-activated protein kinase kinase. *Breast Cancer Res*. 2014;16(5):430. doi:10.1186/s13058-014-0492-925212826
54. Rimawi MF, Wiechmann LS, Wang Y-C, et al. Reduced dose and intermittent treatment with lapatinib and trastuzumab for potent blockade of the HER pathway in HER2/neu-overexpressing breast tumor xenografts. *Clin Cancer Res*. 2011;17(6):1351–1361. doi:10.1158/1078-0432.CCR-10-190521138857
55. Takeshita T, Yamamoto Y, Yamamoto-Ibusuki M, et al. Analysis of ESR1 and PIK3CA mutations in plasma cell-free DNA from ER-positive breast cancer patients. *Oncotarget*. 2017;8(32):52142. doi:10.18632/oncotarget.1847928881720

56. Van Loo P, Wedge D, Nik-Zainal S, Stratton M, Futreal P, Campbell P. 5 proffered paper: the life history of 21 breast cancers. *Eur J Cancer*. 2012;48:S2. doi:10.1016/S0959-8049(12)70709-8
57. Takeshita T, Yamamoto Y, Yamamoto-Ibusuki M, et al. Droplet digital polymerase chain reaction assay for screening of ESR1 mutations in 325 breast cancer specimens. *Transl Res*. 2015;166(6):540–53. e2. doi:10.1016/j.trsl.2015.09.00326434753
58. Perez EA. Treatment strategies for advanced hormone receptor-positive and human epidermal growth factor 2-negative breast cancer: the role of treatment order. *Drug Resist Update*. 2016;24:13–22. doi:10.1016/j.drup.2015.11.001
59. Zanardi E, Bregni G, De Braud F, Di Cosimo S, editors. Better together: targeted combination therapies in breast cancer. *Semin Oncol*. 2015. Elsevier. doi:10.1053/j.seminoncol.2015.09.029
60. Garber JE, Halabi S, Tolaney SM, et al. Factor V Leiden mutation and thromboembolism risk in women receiving adjuvant tamoxifen for breast cancer. *J Natl Cancer Inst*. 2010;102(13):942–949. doi:10.1093/jnci/djq21120554945
61. Onitilo AA, McCarty CA, Wilke RA, et al. Estrogen receptor genotype is associated with risk of venous thromboembolism during tamoxifen therapy. *Breast Cancer Res Treat*. 2009;115(3):643–650. doi:10.1007/s10549-008-0264-219082882
62. Conway K, Parrish E, Edmiston SN, et al. The estrogen receptor-α A908G (K303R) mutation occurs at a low frequency in invasive breast tumors: results from a population-based study. *Breast Cancer Res*. 2005;7(6):R871. doi:10.1186/bcr94916280033
63. Roodi N, Bailey LR, Kao W-Y, et al. Estrogen receptor gene analysis in estrogen receptor-positive and receptor-negative primary breast cancer. *Jnci*. 1995;87(6):446–451. doi:10.1093/jnci/87.6.4467861463
64. Weinreb I, Piscuoglio S, Martelotto LG, et al. Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. *Nat Genet*. 2014;46(11):1166. doi:10.1038/ng.289525240283
65. Ross JS, Gay LM, Wang K, et al. Nonamplification ERBB2 genomic alterations in 5605 cases of recurrent and metastatic breast cancer: an emerging opportunity for anti-HER2 targeted therapies. *Cancer*. 2016;122(17):2654–2662. doi:10.1002/cncr.3010227284958
66. Carter P, Presta L, Gorman CM, et al. Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc National Acad Sci*. 1992;89(10):4285–4289. doi:10.1073/pnas.89.10.4285
67. Gajria D, Chandarlapaty S. HER2-amplified breast cancer: mechanisms of trastuzumab resistance and novel targeted therapies. *Expert Rev Anticancer Ther*. 2011;11(2):263–275. doi:10.1586/era.10.22621342044
68. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–792. doi:10.1056/NEJM200103153441101112481 53
69. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic

breast cancer. *J Clin Oncol*. 2002;20(3):719–726. doi:10.1200/JCO.2002.20.3.71911821453
70. Jahanzeb M. Adjuvant trastuzumab therapy for HER2-positive breast cancer. *Clin Breast Cancer*. 2008;8(4):324–333. doi:10.3816/CBC.2008.n.03718757259
71. Nahta R, Esteva F. Trastuzumab: triumphs and tribulations. *Oncogene*. 2007;26(25):3637. doi:10.1038/sj.onc.121037917530017
72. Bedard PL, de Azambuja E, Cardoso F. Beyond trastuzumab: overcoming resistance to targeted HER-2 therapy in breast cancer. *Curr Cancer Drug Targets*. 2009;9(2):148–162.19275756
73. Rimawi MF, Schiff R, Osborne CK. Targeting HER2 for the treatment of breast cancer. *Annu Rev Med*. 2015;66:111–128.
74. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. *Nat Rev Clin Oncol*. 2012;9(1):16. doi:10.1038/nrclinonc.2012.154
75. Yamaguchi H, Chang S, Hsu J, Hung M. Signaling cross-talk in the resistance to HER family receptor targeted therapy. *Oncogene*. 2014;33(9):1073. doi:10.1038/onc.2013.7423542173
76. Arribas J, Baselga J, Pedersen K, Parra-Palau JL. p95HER2 and breast cancer. *Cancer Res*. 2011;71(5):1515–1519. doi:10.1158/0008-5472.CAN-10-379521343397
77. Castiglioni F, Tagliabue E, Campiglio M, Pupa S, Balsari A, Menard S. Role of exon-16-deleted HER2 in breast carcinomas. *Endocr Relat Cancer*. 2006;13(1):221–232. doi:10.1677/erc.1.0104716601290
78. Mitra D, Brumlik MJ, Okamgba SU, et al. An oncogenic isoform of HER2 associated with locally disseminated breast cancer and trastuzumab resistance. *Mol Cancer Ther*. 2009;8(8):2152–2162. MCT-09-0295.
79. Funes M, Miller JK, Lai C, Carraway KL, Sweeney C. The mucin Muc4 potentiates neuregulin signaling by increasing the cell-surface populations of ErbB2 and ErbB3. *J Biol Chem*. 2006;281(28):19310–19319. doi:10.1074/jbc.M60322520016690615
80. Price-Schiavi SA, Jepson S, Li P, et al. Rat Muc4 (sialomucin complex) reduces binding of anti-ErbB2 antibodies to tumor cell surfaces, a potential mechanism for herceptin resistance. *Int J Cancer*. 2002;99(6):783–791. doi:10.1002/ijc.1041012115478
81. de Melo Gagliato D, Jardim DLF, Marchesi MSP, Hortobagyi GN. Mechanisms of resistance and sensitivity to anti-HER2 therapies in HER2+ breast cancer. *Oncotarget*. 2016;7(39):64431.26824988
82. Ferrari A, Vincent-Salomon A, Pivot X, et al. A whole-genome sequence and transcriptome perspective on HER2-positive breast cancers. *Nat Commun*. 2016;7:12222. doi:10.1038/ncomms1222227406316
83. Kovtun YV, Goldmacher VS. Cell killing by antibody–drug conjugates. *Cancer Lett*. 2007;255(2):232–240. doi:10.1016/j.canlet.2007.04.01017553616
84. Barok M, Joensuu H, Isola J. Trastuzumab emtansine: mechanisms of action and drug resistance. *Breast Cancer Res*. 2014;16(2):209. doi:10.1186/s13058-014-0492-924887180

85. Van Herpen C, Banerji U, Mommers E, et al. 333 Phase I dose-escalation trial with the DNA-alkylating anti-HER2 antibody-drug conjugate SYD985. *Eur J Cancer*. 2015;51:S65. doi:10.1016/S0959-8049(16)30197-6
86. Medina PJ, Goodin S. Lapatinib: a dual inhibitor of human epidermal growth factor receptor tyrosine kinases. *Clin Ther*. 2008;30(8):1426–1447. doi:10.1016/j.clinthera.2008.08.00818803986
87. Tevaarwerk AJ, Kolesar JM. Lapatinib: A small-molecule inhibitor of epidermal growth factor receptor and human epidermal growth factor receptor-2 tyrosine kinases used in the treatment of breast cancer. *Clin Ther*. 2009;31:2332–2348. doi:10.1016/j.clinthera.2009.11.02920110044
88. Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res*. 2006;66(3):1630–1639. doi:10.1158/0008-5472.CAN-05-118216452222
89. Vicario R, Peg V, Morancho B, et al. Patterns of HER2 gene amplification and response to anti-HER2 therapies. *PLoS One*. 2015;10(6):e0129876. doi:10.1371/journal.pone.012987626075403
90. Hafizi S, Dahlbäck B. Signalling and functional diversity within the Axl subfamily of receptor tyrosine kinases. *Cytokine Growth Factor Rev*. 2006;17(4):295–304. doi:10.1016/j.cytogfr.2006.04.00416737840
91. Franklin MC, Carey KD, Vajdos FF, Leahy DJ, De Vos AM, Sliwkowski MX. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell*. 2004;5(4):317–328.15093539
92. Agus DB, Gordon MS, Taylor C, et al. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. *J clin oncol*. 2005;23(11):2534–2543. doi:10.1200/JCO.2005.03.18415699478
93. Leung W-Y, Roxanis I, Sheldon H, et al. Combining lapatinib and pertuzumab to overcome lapatinib resistance due to NRG1-mediated signalling in HER2-amplified breast cancer. *Oncotarget*. 2015;6(8):5678. doi:10.18632/oncotarget.329625691057
94. Hyman D, Piha-Paul S, Rodón J, et al. editors. Neratinib for ERBB2 mutant, HER2 non-amplified, metastatic breast cancer: preliminary analysis from a multicenter, open-label, multi-histology phase II basket trial. *Cancer Res*. 2016. AMER ASSOC CANCER RESEARCH 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA …. doi:10.1158/1538-7445.SABCS15-PD5-05
95. Subramaniam D, He A R, Hwang J, et al. Irreversible multitargeted ErbB family inhibitors for therapy of lung and breast cancer. *Curr Cancer Drug Targets*. 2014;14(9):775–793. doi:10.2174/1568009614666141111104643
96. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016;17(3):367–377. doi:10.1016/S1470-2045(15)00551-326874901
97. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene*. 2008;27(34):4702. doi:10.1038/onc.2008.10918408761
98. Hurvitz SA, Shatsky R, Harbeck N. Afatinib in the treatment of breast cancer. *Expert Opin Investig Drugs*. 2014;23(7):1039–1047. doi:10.1517/13543784.2014.924505

99. Gunzer K, Joly F, Ferrero J-M, et al. A phase II study of afatinib, an irreversible ErbB family blocker, added to letrozole in patients with estrogen receptor-positive hormone-refractory metastatic breast cancer progressing on letrozole. *Springerplus*. 2016;5(1):45. doi:10.1186/s40064-015-1601-726835225
100. Judes G, Rifaï K, Daures M, et al. High-throughput «Omics» technologies: new tools for the study of triple-negative breast cancer. *Cancer Lett*. 2016;382(1):77–85. doi:10.1016/j.canlet.2016.03.00126965997
101. Telli ML, Hellyer J, Audeh W, et al. Homologous recombination deficiency (HRD) status predicts response to standard neoadjuvant chemotherapy in patients with triple-negative or BRCA1/2 mutation-associated breast cancer. *Breast Cancer Res Treat*. 2018;168(3):625–630. doi:10.1007/s10549-017-4624-729275435
102. Shah SP, Roth A, Goya R, et al. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature*. 2012;486(7403):395. doi:10.1038/nature1093322495314
103. Foedermayr M, Sebesta M, Rudas M, et al. BRCA-1 methylation and TP53 mutation in triple-negative breast cancer patients without pathological complete response to taxane-based neoadjuvant chemotherapy. *Cancer Chemother Pharmacol*. 2014;73(4):771–778. doi:10.1007/s00280-014-2404-124526178
104. Birgisdottir V, Stefansson OA, Bodvarsdottir SK, Hilmarsdottir H, Jonasson JG, Eyfjord JE. Epigenetic silencing and deletion of the BRCA1 gene in sporadic breast cancer. *Breast Cancer Res*. 2006;8(4):R38. doi:10.1186/bcr152216846527
105. Gudmundsdottir K, Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene*. 2006;25(43):5864. doi:10.1038/sj.onc.120987416998501
106. O'Shaughnessy J, Schwartzberg L, Danso M, et al. A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). *J Clin Oncol*. 2011;29(15_suppl):1007. doi:10.1200/jco.2011.29.15_suppl.100721205758
107. Patel AG, De Lorenzo SB, Flatten KS, Poirier GG, Kaufmann SH. Failure of iniparib to inhibit poly (ADP-Ribose) polymerase in vitro. *Clin Cancer Res*. 2012;15;18(6):1655–1662.
108. Reles A, Wen WH, Schmider A, et al. Correlation of p53 mutations with resistance to platinum-based chemotherapy and shortened survival in ovarian cancer. *Clin Cancer Res*. 2001;7(10):2984–2997.11595686
109. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. *Breast Cancer Chemosensitivity*. 2007;608:1–22.
110. Gewirtz D. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. *Biochem Pharmacol*. 1999;57(7):727–741. doi:10.1016/S0006-2952(98)00307-410075079
111. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev*. 2004;56(2):185–229. doi:10.1124/pr.56.2.615169927

112. Senchenkov A, Litvak DA, Cabot MC. Targeting ceramide metabolism—a strategy for overcoming drug resistance. *J Natl Cancer Inst*. 2001;93(5):347–357.11238696
113. Chen G, J-P J, Fleming WH, Durán GE, Sikic BI. Prevalence of multidrug resistance related to activation of the mdr1 gene in human sarcoma mutants derived by single-step doxorubicin selection. *Cancer Res*. 1994;54(18):4980–4987.7915196
114. Larsen AK, Skladanowski A. Cellular resistance to topoisomerase-targeted drugs: from drug uptake to cell death. *Biochim Biophys Acta*. 1998;1400(1–3):257–274. doi:10.1016/S0167-4781(98)00140-79748618
115. Withoff S, De SJ, De EV, Mulder N. Human DNA topoisomerase II: biochemistry and role in chemotherapy resistance. *Anticancer Res*. 1996;16(4A):1867–1880.8712715
116. Finlay GJ, Baguley BC, Snow K, Judd W. Multiple patterns of resistance of human leukemia cell sublines to amsacrine analogues. *Jnci*. 1990;82(8):662–667. doi:10.1093/jnci/82.8.6622157028
117. Seidman AD, Reichman BS, Crown J, et al. Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. *J Clin Oncol*. 1995;13(5):1152–1159. doi:10.1200/JCO.1995.13.5.11527537798
118. Wilson WH, Berg SL, Bryant G, et al. Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase I/II trial of 96 hr infusion. *J Clin Oncol*. 1994;12(8):1621–1629. doi:10.1200/JCO.1994.12.8.16217913721
119. Anderson H, Hopwood P, Prendiville J, Radford JA, Thatcher N, Ashcroft L. A randomised study of bolus vs continuous pump infusion of ifosfamide and doxorubicin with oral etoposide for small cell lung cancer. *Br J Cancer*. 1993;67(6):1385. doi:10.1038/bjc.1993.2568390287
120. Bristol-Myers Squibb. *Taxol® (paclitaxel) [Prescribing information]*. New York: Bristol-Myers Squibb; 2011.
121. Greenberger L, Williams SS, Horwitz SB. Biosynthesis of heterogeneous forms of multidrug resistance-associated glycoproteins. *J Biol Chem*. 1987;262(28):13685–13689.2888763
122. Tolcher A, Cowan K, Solomon D, et al. Phase I crossover study of paclitaxel with r-verapamil in patients with metastatic breast cancer. *J clin oncol*. 1996;14(4):1173–1184. doi:10.1200/JCO.1996.14.4.11738648372
123. Twelves C, Jove M, Gombos A, Awada A. Cytotoxic chemotherapy: still the mainstay of clinical practice for all subtypes metastatic breast cancer. *Crit Rev Oncol Hematol*. 2016;100:74–87. doi:10.1016/j.critrevonc.2016.01.02126857987
124. Jameson GS, Hamm JT, Weiss GJ, et al. A multicenter, phase I, dose-escalation study to assess the safety, tolerability, and pharmacokinetics of etirinotecan pegol in patients with refractory solid tumors. *Clin Cancer Res*. 2013;19(1):268–278. doi:10.1158/1078-0432.CCR-12-120123136196
125. Hoch U, Staschen C-M, Johnson RK, Eldon MA. Nonclinical pharmacokinetics and activity of etirinotecan pegol (NKTR-102), a long-acting topoisomerase 1 inhibitor, in multiple cancer models. *Cancer Chemother Pharmacol*. 2014;74(6):1125–1137. doi:10.1007/s00280-014-2577-725228368

126. Huennekens F. The methotrexate story: a paradigm for development of cancer chemotherapeutic agents. *Adv Enzyme Regul*. 1994;34:397–419.7942284
127. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer*. 2003;3(5):330. doi:10.1038/nrc107412724731
128. Grant SC, Kris MG, Young CW, Sirotnak FM. Edatrexate, an antifolate with antitumor activity: a review. *Cancer Invest*. 1993;11(1):36–45.8422595
129. Sirotnak F, Moccio D, Kelleher L, Goutas L. Relative frequency and kinetic properties of transport-defective phenotypes among methotrexate-resistant L1210 clonal cell lines derived in vivo. *Cancer Research*. 1981;41(11 Pt 1):4447–4452.
130. Kool M, Van Der Linden M, de Haas M, et al. MRP3, an organic anion transporter able to transport anti-cancer drugs. *Proc National Acad Sci*. 1999;96(12):6914–6919. doi:10.1073/pnas.96.12.6914
131. Hooijberg J, Broxterman H, Scheffer G, et al. Potent interaction of flavopiridol with MRP1. *Br J Cancer*. 1999;81(2):269. doi:10.1038/sj.bjc.669068710496352
132. Cowan KH, Jolivet J. A methotrexate-resistant human breast cancer cell line with multiple defects, including diminished formation of methotrexate polyglutamates. *J Biol Chem*. 1984;259(17):10793–10800.6206061
133. Volk EL, Rohde K, Rhee M, et al. Methotrexate cross-resistance in a mitoxantrone-selected multidrug-resistant MCF7 breast cancer cell line is attributable to enhanced energy-dependent drug efflux. *Cancer Res*. 2000;60(13):3514–3521.10910063
134. Ohmori T, Podack E, Nishio K, et al. Apoptosis of lung cancer cells caused by some anti-cancer agents (MMC, CPT-11, ADM) is inhibited by bcl-2. *Biochem Biophys Res Commun*. 1993;192(1):30–36.8476431
135. Priest DG, Ledford BE, Doig MT. Increased thymidylate synthetase in 5-fluorodeoxyuridine resistant cultured hepatoma cells. *Biochem Pharmacol*. 1980;29(11):1549–1553.6446915
136. Spears CP. Clinical resistance to antimetabolites. *Hematol Oncol Clin North Am*. 1995;9(2):397–414.7642470
137. Klatt O, Stehlin JS, McBride C, Griffin A. The effect of nitrogen mustard treatment on the deoxyribonucleic acid of sensitive and resistant Ehrlich tumor cells. *Cancer Res*. 1969;29(2):286–290.5765411
138. Ichiro N, Kimitoshi K, Junko K, et al. Analysis of structural features of dihydropyridine analogs needed to reverse multidrug resistance and to inhibit photoaffinity labeling of P-glycoprotein. *Biochem Pharmacol*. 1989;38(3):519–527.2563655
139. Zamble DB, Lippard SJ. Cisplatin and DNA repair in cancer chemotherapy. *Trends Biochem Sci*. 1995;20(10):435–439.8533159
140. Perez R. Cellular and molecular determinants of cisplatin resistance. *Eur J Cancer*. 1998;34(10):1535–1542.9893624
141. Moudi M, Go R, Yien CYS, Nazre M. Vinca alkaloids. *Int J Prev Med*. 2013;4(11):1231.24404355
142. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Adv Drug Deliv Rev*. 2013;65(1):36–48. doi:10.1016/j.addr.2012.09.03723036225

143. Coyle C, Cafferty F, Vale C, Langley R. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. *Ann Oncol*. 2016;27(12):2184–2195. doi:10.1093/annonc/mdw41027681864
144. Zhang J, Li G, Chen Y, et al. Metformin Inhibits tumorigenesis and tumor growth of breast cancer cells by upregulating miR-200c but downregulating AKT2 expression. *J Cancer*. 2017;8(10):1849. doi:10.7150/jca.1985828819383
145. Al-Zaidan L, Ruz E, Abu R, Malki AM. Screening novel molecular targets of metformin in breast cancer by proteomic approach. *Front Public Health*. 2017;5:277. doi:10.3389/fpubh.2017.0008129085821
146. Obaidi J, Musallam E, Al-Ghzawi HM, Azzeghaiby SN, Alzoghaibi IN. Vitamin D and its relationship with breast cancer: an evidence based practice paper. *Glob J Health Sci*. 2015;7(1):261.
147. Gall TL, Kristjansson E, Charbonneau C, Florack P. A longitudinal study on the role of spirituality in response to the diagnosis and treatment of breast cancer. *J Behav Med*. 2009;32(2):174–186. doi:10.1007/s10865-008-9182-318982441
148. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Rev Clin Onco*. 2008;5(8):466. doi:10.1038/ncponc1134
149. MacArthur AC, Le ND, Abanto ZU, Gallagher RP. Occupational female breast and reproductive cancer mortality in British Columbia, Canada, 1950–94. *Occup Med (Chic Ill)*. 2007;57(4):246–253. doi:10.1093/occmed/kqm002
150. Akbari ME, Kashani FL, Ahangari G, et al. The effects of spiritual intervention and changes in dopamine receptor gene expression in breast cancer patients. *Breast Cancer*. 2016;23(6):893–900. doi:10.1007/s12282-015-0658-z26597879
151. Hejazi SH, Ahangari G, Pornour M, et al. Evaluation of gene expression changes of serotonin receptors, 5-HT3AR and 5-HT2AR as main stress factors in breast cancer patients. *Asian Pac J Cancer Prev*. 2013;15(11):4455–4458. doi:10.7314/APJCP.2014.15.11.4455
152. Urbaniak C, Gloor GB, Brackstone M, Scott L, Tangney M, Reid G. The microbiota of breast tissue and its association with tumours. *Appl Environ Microbiol*. 2016;AEM: 01235–16.
153. Toga AW, Foster I, Kesselman C, et al. Big biomedical data as the key resource for discovery science. *JAMIA*. 2015;22(6):1126–1131. doi:10.1093/jamia/ocv07726198305
154. Kanehisa M, Goto S. KEGG: Breast cancer - Reference pathway; 2018 Available at: https://www.genome.jp/kegg-bin/show_pathway?map05224. Accessed May 15, 2019
155. Jeibouei, S., Akbari, M. E., Kalbasi, A., Aref, A. R., Ajoudanian, M., Rezvani, A., & Zali, H. (2019). Personalized medicine in breast cancer: pharmacogenomics approaches. *Pharmacogenomics and personalized medicine*, 59-73.