Advances in predicting breast cancer driver mutations: Tools for precision oncology (Review)

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Abstract. In the modern era of medicine, prognosis and treatment, options for a number of cancer types including breast cancer have been improved by the identification of cancer-specific biomarkers. The availability of high-throughput sequencing and analysis platforms, the growth of publicly available cancer databases and molecular and histological profiling facilitate the development of new drugs through a precision medicine approach. However, only a fraction of patients with breast cancer with few actionable mutations typically benefit from the precision medicine approach. In the present review, the current development in breast cancer driver gene identification, actionable breast cancer mutations, as well as the available therapeutic options, challenges and applications of breast precision oncology are systematically described. Breast cancer driver mutation-based precision oncology helps to screen key drivers involved in disease development and progression, drug sensitivity and the genes responsible for drug resistance. Advances in precision oncology will provide more targeted therapeutic options for patients with breast cancer, improving disease-free survival and potentially leading to significant successes in breast cancer treatment in the near future. Identification of driver mutations has allowed new targeted therapeutic approaches in combination with standard chemo- and immunotherapies in breast cancer. Developing new driver mutation identification strategies will help to define new therapeutic targets and improve the overall and disease-free survival of patients with breast cancer through efficient medicine.

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Contents

1. Introduction

Cancer initiation and progression is a long and complex biological phenomenon caused by any significant alterations in the genome, proteome and chromatin or in any other cellular levels. In total, 10-30% of breast cancer cases are genetically inherited, 5-10% of cases are strongly correlated with hereditary factors and nearly 5% of cases are caused by high penetrance gene mutations such as *BRCA1, BRCA2, TP53, CDH1, STK11* and *LKB1* (1,2). Among these high-penetrance

genes, *BRCA1* and *BRCA2* are the most crucial genes involved in the regulation of DNA repair, transcription and the cell cycle. Somatic/germline mutations in these two genes are associated with breast cancer and are considered the strongest susceptibility markers that have been identified, with a 45-80% life-time risk in breast cancer in various ethnic and generalized population levels (3-5). A number of these mutations are largely from somatic cells and the majority are neutral/passenger mutations, while certain mutations are more harmful (driver mutations) and give specific cellular advantage, leading to cell proliferation (6-8). Due to the increasing prevalence of high-throughput next-generation sequencing (whole genome, exome and targeted sequencing), the genomic information of thousands of tumors from various cancer types can help researchers to identify and characterize cancer samples in an easier and more robust way (9-11). Besides, increasing the amount of cancer sequencing data is also helpful to find ways to treat patients using multiple approaches. One such approach is driver gene mutation identification and treatment. To date, mutational recurrence in patients is a highly reliable gene marker for driver gene identification (12).

Most driver genes are cancer or subtype specific, so identification of specific cancer drivers is an important step in cancer therapy (13). Additionally, these driver mutations lead to structural and functional consequences that could lead to tumor heterogeneity and drug resistance (14-16). Thus, identifying key driver mutations is a prominent method for disease diagnosis and management. However, identifying those key players is cumbersome with insufficient tumor information (including low coverage and sequence bias), a complex tumor microenvironment, intra/inter-tumor heterogeneity and other biological issues (17). In recent years, several dedicated cancer biology studies have made numerous notable contributions including large cancer sequence depositories such as The Cancer Genome Atlas (TCGA; https://portal.gdc.cancer.gov/), COSMIC database (https://cancer.sanger.ac.uk/cosmic) and International Cancer Genome Consortium (ICGC; https://icgc.org/), and several versatile sequence analysis tools and servers (18). However, conventional treatments and their outcomes are highly limited due to the diversity of patient genome profiles (19,20). Hence, identification of patient-specific treatment plans (precision oncology) is in urgent need for cancer therapy (21,22).

A pharmacogenomics-based treatment strategy is the most advanced and effective. Genetic testing (including DNA sequencing technology) can identify specific mutational alterations related to cancer, which is most likely to be helpful in the development of a patient-specific treatment plan when the patient does not respond to standard therapy. However, chemotherapeutic agents with a narrow therapeutic window and adverse drug toxicities are life-threatening (23). Breast cancer targeted therapies generally target a specific gene or protein and show an improved biological response to the disease with minimal side effects. Precision cancer therapy makes clinical decisions based on the identification of targets using genomic/proteomics data (24). Therefore, cancer treatment will be improved by increasing the amount of tumor genomic data, including mutation, methylation and expression data (25). One of the standard precision oncology approaches is treating patients with cancer based on subtyping (26). Besides, targeting the most actionable, identified and reported driver gene mutations in several cancer samples will help to treat patients in the new paradigm of breast cancer precision medicine (27-29). Furthermore, several additional metrics are needed to further identify driver genes for understanding precision oncology treatment (Fig. 1). In the present review, several breast cancer-associated driver genes, existing strategies in driver gene identification, actionable targets, various existing challenges and applications of precision oncology in breast cancer prognosis and treatment are covered.

2. Computational identification of breast cancer driver mutations

The identification of breast cancer drivers is the initial step in targeted therapy. Cancer driver identification strategies are evolving, and several tools are being developed, including sequence-based cancer driver prediction tools such as MutSigCV (30), Mutation Set Enrichment Analysis (31), OncodriveFML (32), OncodriveCLUST (33), MuSiC2 (34) and ActiveDriver (35) Similarly, several tools have been developed to predict mutation consequences at the protein level including Sorting Intolerant From Tolerant (SIFT) (36), Polymorphism Phenotyping v2 (PolyPhen-2) (37), CanDrA (38), CHASM (39) and MutationAssessor (40). Several breast cancer drivers are identified and classified based on their occurrence in cancer, their histological and molecular functions and regulatory properties (41). Most cancer drivers have an oncogene, tumor suppressor or dual gene role (42). Even a single mutation in a driver gene may cause diverse effects and show differential tumorigenic and drug response potentials in patients with cancer (43).

Additionally, several computational programs and servers contribute to identifying key driver mutations for precision oncology. Along with germline mutations, numerous somatic variants are being detected by several efficient tools including MuTect (https://github.com/broadinstitute/mutect), VarScan (http://varscan.sourceforge.net/), GATK variant calling pipeline (https://software.broadinstitute.org/gatk/), Torrent variant caller (http://coolgenes.cahe.wsu.edu/ion-docs/Torrent-Variant-Caller-Plugin.html), DeepVariant (https://github.com/google/deepvariant) and Strelka (https://github.com/Illumina/strelka). These tools facilitate the identification of somatic mutations in a robust manner. HotSpot3D (https://github.com/ding-lab/hotspot3d), Cancer3D (http://cancer3d.org/), AlloDriver (https://mdl.shsmu.edu.cn/ALD/), SGDriver (44), CLUMPs (45) and 20/20+ (46) are being used to predict mutational impacts at the 3D structural and conformational level.

3. Actionable breast cancer driver mutations and the available drugs

Genome and proteome level data are screened for mutations and their corresponding protein level impacts are assessed using high-throughput technologies. However, only <10% of mutations are actionable, hence targeting only actionable mutations may not be beneficial in certain patients and thus lead to a poor response to therapy (47). Several public oncogenomic databases such as TCGA (48), IGC and cBioportal

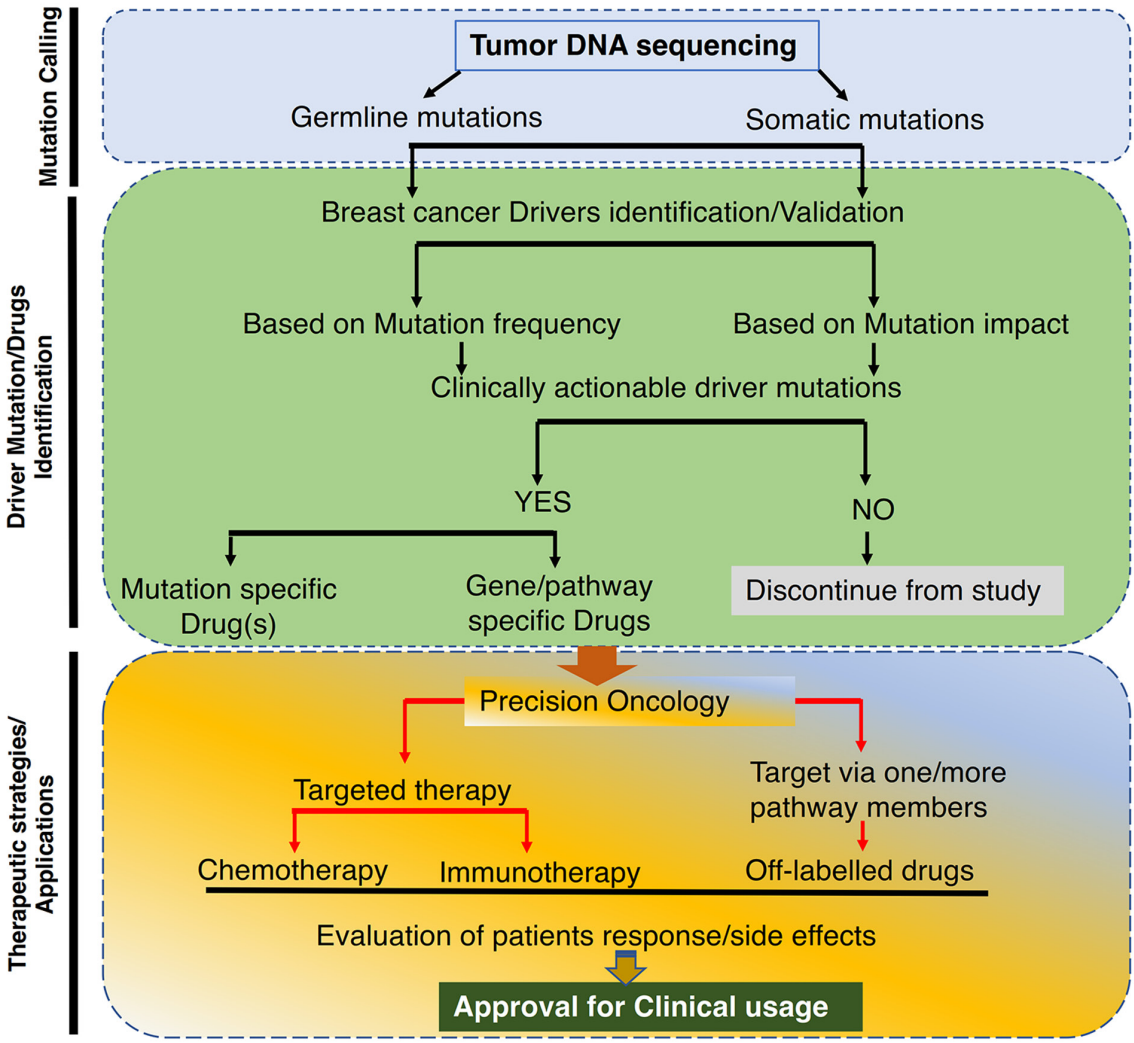

Figure 1. Flowchart illustrating the identification of breast cancer driver gene mutations and their role in precision oncology.

(www.cbioportal.org) provide large scale multi-level information that can be used in research to facilitate disease prognosis, prevention and drug discovery (49). Several targetable breast cancer mutations including oncogenic, truncating, amplifications and fusions have been identified, and these mutations and their corresponding U.S. Food and Drug Administration (FDA)-approved drugs are listed in Table I and detailed information about key gene mutations and targeted drugs can be accessed using OncoKB, a data resource for precision oncology (www.oncokb.org).

Trastuzumab is a widely tested drug against breast cancer and understanding the action and resistance of this drug will help to develop new viable therapeutic approaches (50). Several key pathways such as the *AKT, mTOR, PIK3CA* and cell regulation pathways, and numerous variants of tyrosine kinase receptors are targeted for drug discovery and development. A study has demonstrated that the resistance mechanism of trastuzumab is potentially caused by the insulin-like growth factor I (IGF-1) receptor and mutation of IGF-1 shows a significant level of drug resistance against trastuzumab (51). A high percentage of somatic mutations in *TP53, PI3KCA, PTEN and AKT* have been identified in breast cancer. Several large level mutational landscape studies have paved the way to identify subgroup-specific sensitivities in these pathways (52,53). Of the hotspot mutations identified in the most commonly mutated gene, PIK3CA (~25%), 80-90% of mutations occur in exon9 (E545K/E542K) and three hotspot mutations occur in exon 20 (54).

4. Targetable kinase family driver mutations and multi-kinase inhibitors in breast cancer precision therapy

The epidermal growth factor receptor (*EGFR*) is another proven significant target in several cancer types, and a number of inhibitors are designed and used for *EGFR*-specific gene mutations including gefitinib, erlotinib, trastuzumab and afatinib (55-58). Similarly, in breast cancer, the tyrosine-kinase activity domain of *HER2* is prone to pathogenic mutations. Several key *HER2* activating somatic mutations have been identified, including G309A, D769H/Y, V777L, P780ins, V842i and R896C (59). Tumors harboring the T798M *HER2* mutation can be treated with kinase inhibitors such as lapatinib or trastuzumab (60). Similarly, other *HER2* mutations including the L755S, T798I and L869R mutations and several duplication events including S310, V777 and Y772-A775dup are treated with neratinib (61-63). By contrast, a known EGFR inhibitor,

Table I. Key actionable breast cancer mutations and their FDA approved drugs.

Genes	Mutations	FDA approved drugs
NTRK1	G595R	Larotrectinib
NTRK3	G623R	Larotrectinib
BRAF	K601, L597, G464, G469A, G469R and G469V	PLX8394
CDK12	Truncating mutations	Cemiplimab, nivolumab and pembrolizumab
CDKN2A	Oncogenic mutations	Ribociclib, palbociclib and abemaciclib
FGFR1	Oncogenic mutations	BGJ398, AZD4547, erdafitinib and Debio1347
FGFR2	Oncogenic mutations	Erdafitinib, BGJ398, AZD4547 and Debio1347
FGFR3	Oncogenic mutations	Erdafitinib, Debio1347, BGJ398 and AZD4547
KRAS	Oncogenic mutations	Cobimetinib, trametinib and binimetinib
MET	Fusions	Crizotinib
MTOR	Oncogenic mutations	Temsirolimus and everolimus
NF1	Oncogenic mutations	Trametinib and cobimetinib
PTEN	Oncogenic mutations	AZD8186 and GSK2636771
AKT1	E17K	AZD5363
ERBB2	Oncogenic mutations	Neratinib
ESR1	Oncogenic mutations	Fulvestrant and AZD9496
PIK3CA	Oncogenic mutations	Fulvestrant + copanlisib
PIK3CA	Oncogenic mutations	GDC-0077
BRCA1	Oncogenic mutations	Talazoparib
BRCA1	Oncogenic mutations	Olaparib
BRCA2	Oncogenic mutations	Talazoparib
BRCA2	Oncogenic mutations	Olaparib
ERBB2	Amplification	Trastuzumab + lapatinib (or each as a monotherapy), neratinib, ado-trastuzumab emtansine, pertuzumab + trastuzumab, trastuzumab + tucatinib + capecitabine and trastuzumab deruxtecan
NTRK1	Fusions	Larotrectinib and entrectinib
NTRK2	Fusions	Larotrectinib and entrectinib
NTRK3	Fusions	Larotrectinib and entrectinib
PIK3CA	Oncogenic mutations	Alpelisib + ulvestrant

FDA, U.S. Food and Drug Administration.

gefitinib, showed differential response based on *EGFR* heterogeneity in triple negative breast cancer (TNBC) (64). *CDK4* and *CDK6* inhibitors are administered to treat hormone receptor positive breast cancer. A study showed that, cyclin E1 gene amplification and RB transcriptional corepressor 1 (*RB1*) loss in T47D cell lines results in resistance to CDK4/6 inhibitors, and multiple mutations in *RB1* in metastatic breast cancer show resistance to CDK4/6 inhibitors (65,66).

5. Precision oncology approaches for DNA repair defect mutations in breast cancer

Identification of DNA repair defects and their mutational events could help to identify personalized treatment strategies and targets. One such example is *BRCA1*/*BRCA2* mutations or loss, which lead to deficiency in homologous recombination and genomic instability (1,67). *BRCA1* mutations are proportionately higher in TNBC subtypes with several crucial gene mutations considered to be a major risk in young women and crucial for the scientific community for disease prevention and treatment (68). Therefore, identifying and characterizing *BRCA1/2* functions and mutations may help to design personalized approaches to treat patients with breast cancer. Poly-(ADP ribose) polymerase 1 (PARP1) functions as a DNA damage sensor for both single and double-stranded DNA breaks and PARP2 is also responsible for base-excision DNA repair through homo and heterodimerization with PARP1; thus, these two proteins play a significant role in maintaining genomic stability through DNA repair mechanisms (69,70). Deleterious mutations in *BRCA* genes are highly sensitive to PARP1 inhibitors and DNA alkylating agents (71). PARP1 inhibitors intensely reduce DNA single and double-stranded breaks in *BRCA1/2*-deficient tumors, resulting in improved sensitivity to DNA damaging agents such as cisplatin and PARP1 inhibitors, which are typically administered in *BRCA* mutation-associated breast and ovarian cancer (72).

Table II. List of clinical studies in DNA repair defects mutations and their outcomes.

Interventions	Trial ID	Study name	Status	Cancer type/ subtype
Cisplatin + rucaparib	NCT01074970	PARP Inhibition for Triple Negative Breast Cancer ($ER^-/PR^-/HER2^-$)With BRCA1/2 Mutations	Completed	Breast Cancer
Gemcitabine + carboplatin + BSI-201	NCT00813956	A Phase 2 Study of Standard Chemotherapy Plus BSI- 201 (a PARP Inhibitor) in the Neoadjuvant Treatment of Triple Negative Breast Cancer	Completed	Triple negative breast cancer
AZ2281 + carboplatin	NCT01445418	AZD2281 Plus Carboplatin to Treat Breast and Ovarian Cancer	Completed	Breast and ovarian Cancer
AZD2171 + fulvestrant	NCT00454805	AZD2171 in Addition to Fulvestrant in Patients With Advanced Breast Cancer	Completed	Advanced breast cancer
PARP inhibitor 2X-121	NCT03562832	Investigation of Anti-tumour Effect and Tolerability of the PARP Inhibitor 2X-121 in Patients With Metastatic Breast Cancer Selected by the 2X-121 DRP	Recruiting	Metastatic breast cancer
Talazoparib	NCT03990896	Evaluation of Talazoparib, a PARP Inhibitor, in Patients With Somatic BRCA Mutant Metastatic Breast Cancer: Genotyping Based Clinical Trial	Recruiting	Breast cancer
Rucaparib	NCT03911453	Window of Opportunity Trial, PARP Inhibitor Rucaparib Affect on PD-L1 Expression in Triple Negative Breast Tumors	Recruiting	Breast cancer
Talazoparib + Sacituzumab Govitecan	NCT04039230	Study to Evaluate Sacituzumab Govitecan in Combination With Talazoparib in Patients With Metastatic Breast Cancer	Recruiting	Breast cancer
Niraparib + Trastuzumab	NCT03368729	Niraparib in Combination With Trastuzumab in Metastatic $HER2^+$ Breast Cancer	Recruiting	Metastatic $breast^+$ cancer and HER2 breast carcinoma
Olaparib + Paclitaxel and Carboplatin	NCT03150576	Platinum and Polyadenosine 5'Diphosphoribose Polymerisation (PARP) Inhibitor for Neoadjuvant Treatment of Triple Negative Breast Cancer (TNBC) and/or Germline BRCA (gBRCA) Positive Breast Cancer	Recruiting	Breast cancer
Lynparza	NCT04041128	PARP Inhibition During Pre-surgical Window in Breast/Ovary Cancer	Recruiting	Ovarian and breast cancer

Trabectedin is another inhibitor recently approved in Europe and North Korea for the treatment of soft tissue sarcomas including breast, ovarian, prostate and other solid tumors. Trabectedin functions by targeting the minor grooves of DNA, bending the DNA toward the major grooves through which it increases therapeutic efficiency by blocking transcription coupled nucleotide excision repair machinery, leading to cell death (73-75). A previous study demonstrated that the PARP1 inhibitor, olaparib, combined with cediranib potentially inhibits homology-directed DNA repair via *BRCA1/2* and *RAD51* downregulation and significantly improves progression-free survival (76,77). A list of drugs used for DNA repair defects at various levels of clinical trials are listed in Table II (74,78-88). These inhibitors mainly target DNA repair pathways in *BRCA1/2* mutant/deficient breast cancer.

6. Targeting breast cancer driver mutations by immunotherapy

Several breast and other cancer drivers can be treated using different strategies, including combination therapy (double or triple combination), by targeting more than one genetic

event (mutations/mutations plus copy number events or mutations plus upregulation), which improves antitumor potential (89-91). The efficacy of immunotherapies are tested with positive outcomes in both primary and metastatic tumors and are the most potent alternatives to the cytotoxic chemo- and radiotherapies (92). Immunotherapy enhances both progression-free and overall survival and prevents disease recurrence in patients with breast cancer by targeting specific genes or pathways. Checkpoint inhibition is a known approach used in cancer treatment, which targets certain checkpoint molecules such as programmed cell death protein 1, programmed death-ligand 1 (PD-L1) and CTLA4 (93,94). Atezolizumab is an FDA approved PD-L1 antibody for the treatment of metastatic TNBC along with other cancer types (95). Trastuzumab is the first antibody used for the treatment of metastatic breast cancer with a gene amplification or upregulation of CD340 and HER2 (96). At present, several anti-HER2 inhibitors including afatinib, lapatinib, gefitinib and neratinib are used alone or in combination with several monoclonal antibodies and chemotherapeutic agents (97). A list of monoclonal antibodies and combined treatments administered for several breast cancer subtypes are listed in Table SI (88,98-122). In recent years, resistance against a number of monoclonal and combination therapies has been observed, hence antibody-drug conjugates (ADCs) have been established to overcome this drug resistance. A T-cell bispecific antibodies approach and an ADC-based FDA-approved drug combination (ado-trastuzumab emtansine) are the most constructive approaches for the treatment of patients with breast cancer (123).

7. Challenges and applications of precision oncology in breast cancer

Overall, ~10% of mutations in breast cancer are deemed actionable, highlighting a significant challenge in the realm of precision oncology. Several vital factors determine tumor growth, immune escape and survival. The T-cell response is the most crucial for identifying tumor cells from the normal cell population to produce antitumor immunity (124,125). This immunogenic potentials may vary from one breast cancer subtype to another (126). Drug efficacy is influenced not only by targeted genes but also by various factors, including genetic variability, individual drug performance and mutations that affect drug metabolism. For instance, cytochrome P450 (CYP) pathway members (including CYP3A4, CYP19A and CYP2D6) have been associated with metabolizing anticancer drugs (127). A recent study revealed that $HER2^+$ breast cancer is more responsive to immunotherapy, but estrogen receptor-negative and $HER2^+$ breast cancer has more immunogenic potential (128). Higher expression of estrogen may lower interferon-γ signaling and human leukocyte antigen gene complex-II expression, which facilitates tumor escape from immune action (129). Besides, estrogens are known to be a risk factor for breast cancer by enhancing several key oncogenic growth factors including EGF, IGF, vascular endothelial growth factor, fibroblast growth factor and their corresponding receptors. An estrogen-high tumor microenvironment plays an important immunosuppressive role for the survival of tumor cells in weak immunogenic tumor cells (98,130,131). Hence, targeting these genes and their active mutations may improve breast cancer prognosis and treatment. Similarly, the use of anti-estrogen therapies combined with aromatase inhibitors could be a better approach to improve the further response to immunotherapies (132).

8. Existing driver mutation prediction approaches and their challenges

The identification of somatic driver genes from germline variants is a crucial step in genomic oncology. In addition to several known germline variants, a growing number of vital somatic variants are being identified. Those somatic variants are validated through modern computational strategies and functional annotation resources including SIFT (36), Polyphen-2 (37), CHASM (39), Mutation Assessor (40), DbNSFP (133) and Mutation Taster (134). However, recent developments in high-throughput techniques and potential computational resources/tools have resulted in very few mutations being clinically actionable. There are major difficulties in differentiating driver from passenger mutations, a lack of strategies to validate genomic variants and challenges associating the clinical relevance of these mutations. Apart from single nucleotide polymorphism, several copy number variations, including copy-number gains and amplifications, and copy-number loss have been identified in breast cancer (135). *BRCA1* is a well-known tumor suppressor gene in breast cancer and identifying the key driver genes in *BRCA1*-associated tumorigenesis will help to predict the road map of this cancer type. In a public sequence repository (cBioportal), ~80 *BRCA1*-mutated/deficient breast cancer types were found, and the majority of mutations belong to deleterious single nucleotide variations and copy number events, including homozygous deletions or amplifications. Among these mutations *TP53* and *MYC* are the most commonly copy number altered driver genes in *BRCA1*-associated tumorigenesis and contributing to over 65 and 40% of cases respectively, highlighting their significant roles in cancer progression and potential for targeted therapies (136). The highest number of *MYC* driver mutations identified in *BRCA1*-associated tumors was in the TNBC subtype. Additionally, the amplification of *MYC* along with the copy number amplification of *PIK3CA* and the loss of copy number in *RB1* and *PTEN,* supports *MYC* amplification and promotes breast tumorigenesis (137,138). However, due to a low number of cases in this cohort, it is challenging to determine the outcomes of these drivers.

9. Role of driver genes in breast cancer prognosis and the tumor microenvironment

Along with genomic data for the prediction of breast cancer driver genes, mRNA expression data plays a crucial role in predicting drivers in disease prognosis and their involvement in the tumor microenvironment (139). A recent study revealed a list of differentially expressed breast cancer driver genes to help predict disease prognosis and overall survival (140). The mRNA expression levels of the most enriched driver genes including *DDX3X, BRD7, CCR7* and *UBE2A* are associated with a higher hazard ratio. Several key breast cancer drivers, in conjunction with the tumor microenvironment, significantly influence treatment response in patients

with breast cancer. These drivers are responsible for tumor heterogeneity and for varied responses to drug (141). In precision oncology, high-throughput sequencing data including genomics, transcriptomics and proteomics data helps to predict the characteristics of patients and the tumor behavior at the genome/proteome level. Tumor heterogeneity is a prime cause for overall patient survival, disease-free survival and response to chemo- or immunotherapy.

10. Conclusions and future perspectives

The identification of driver mutations has allowed for new targeted therapeutic approaches in combination with standard chemo- and immunotherapies in breast cancer. Existing drugs for the identified actionable mutations in breast cancer are also used to treat other cancer types; however, whether these drugs are beneficial to other cancer types is still unclear. For example, trastuzumab, which targets *HER2* amplification/upregulation, is beneficial to both breast and gastric cancer, while it shows no significant results in lung and ovarian cancer (142,143). Even with the developing modern applications in clinical trial design, challenges continue, including tumor cellularity, intra- and inter-tumor heterogeneity and the tumor microenvironment. Hence, identifying new strategies to overcome these challenges and identifying new therapeutic targets/biomarkers will help to improve the overall and disease-free survival of patients through efficient breast cancer medicine. The present review connects the current strategies with future approaches for identifying novel breast cancer drivers, aiming to aid researchers and ultimately benefit patients. Differential drug responses among breast cancer subtypes influence overall efficacy. Therefore, identifying new driver genes, novel susceptibility regions or loci, and alternative pathways will expedite the discovery of new therapeutic targets. The ultimate goal of breast cancer precision oncology is to identify more therapeutic targets and to increase the drug efficacy while reducing toxicity for patients.

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Availability of data and materials

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Authors' contributions

WH and BKR designed this study. WH generated the figure. BKR, WH, TP, JS, YZ, MMS and TC performed the background research. BKR and WH drafted and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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