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Current concepts in breast cancer genomics: An evidence based review by the CGC breast cancer working group

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ABSTRACT

Background: Genomic abnormalities in breast cancer have been described according to diverse conceptual frameworks, including histologic subtypes, clinical molecular subtypes, intrinsic DNA, RNA, and epigenetic profiles, and activated molecular pathways.

Methods: The Cancer Genomics Consortium (CGC) Breast Cancer Workgroup performed an evidence based literature review to summarize current knowledge of clinically significant genomic alterations in breast cancer using CGC levels of evidence. Targetable or disease-defining alterations were prioritized.

Results: We summarized genomic alterations in breast cancer within a framework of existing clinical tools for diagnosis, risk stratification, and therapeutic management. Using CGC levels of evidence, we catalog copy number profiles, gene expression profiles, and mutations in clinically significant genes. We also describe emerging molecular markers such as methylation profiling and immunotherapy biomarkers.

Conclusion: A summary of currently available information on breast cancer genomics will enhance precision medicine by serving as an interpretive resource for clinical laboratory geneticists, providing a foundation for future practice guidelines, and identifying knowledge gaps to address in future research.

Introduction and Background

Current diagnosis and management of breast cancer relies primarily upon histology, clinical and pathologic staging, and a limited set of biomarkers for hormone therapy and anti-HER2 therapy. The principal biomarkers are estrogen receptor alpha (ER-α) (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/neu, *ERBB2*). Pathologic work up of invasive tumors includes immunohistochemistry to evaluate for ER and PR expression, and immunohistochemistry and/or in situ hybridization (ISH) for determination of HER2 status. Histopathology, clinical data, and biomarker data are integrated to determine a patient's prognostic stage group. The clinical prognostic stage group includes all available clinical and imaging data as well as histopathology and biomarker status on the diagnostic breast biopsy and/or distant metastases. The pathologic prognostic stage group incorporates histopathologic findings from surgical resection, including the final tumor size, the status of surgical margins and any excised lymph nodes, and distant metastatic disease, if applicable. In the neoadjuvant setting, therapy is administered after the diagnostic biopsy but before tumor resection, and clinical prognostic staging is employed; the pathologic stage post neoadjuvant treatment is used to assess response to treatment and to guide post-surgery adjuvant treatment. Additional testing for risk stratification and therapeutic management typically includes a proliferation marker (mitotic index and/or Ki67 expression), and for a subset of patients with early stage ER positive, HER2 negative tumors, clinically approved gene expression profiling ("genomic") assays are performed on a tumor sample to determine the risk of tumor recurrence. Surgery is the mainstay of breast cancer treatment, and aside from *HER2* (*ERBB2*) amplification, specific genomic abnormalities are most important in the setting of inoperable or metastatic disease. Genomic profiling is becoming more relevant as additional actionable genetic abnormalities are discovered. This review summarizes recent advances and current concepts in breast cancer genomics.

Methods

We performed a systematic review to identify original articles on human breast cancer genetics or genomics published in priority journals in the English language since 2010. The full search

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Table 1
Cancer Genomics Consortium Levels of Evidence.

Tier	Data Source(s)	Interpretation
1	FDA approved therapies, professional guidelines, multiple large clinical studies	Strong evidence supporting clinical utility of variant(s) for diagnosis, selection of therapies, or predicting disease outcome
2	One large study or multiple case reports	Emerging evidence supporting clinical utility of variant(s)
3	Case reports or expert opinion	Unknown clinical significance
4	Published evidence indicating lack of pathogenicity of variant(s)	Benign or likely benign

strategy performed in the Ovid MEDLINE database is shown in the Data Supplement. Additionally, we manually searched major journals, textbooks, and clinical practice guidelines to capture relevant articles regardless of publication date. We excluded non-malignant neoplasms, non-epithelial neoplasms, and metastases to the breast originating in other organs. We prioritized articles according to size of the study, the inclusion of clinical data, and the clinical significance of the aberrations described. We then triaged articles according to the type of aberration described (DNA copy number, RNA expression profiling, somatic sequence variation, or other mutations).

Somatic variants were categorized at the gene level according to the Cancer Genomics Consortium levels of evidence shown in Table 1. We excluded Tier 3 and Tier 4 variants from this review. We included genes associated with an inherited risk for breast cancer according to current literature and guidelines of the National Comprehensive Cancer Network (NCCN) because inherited mutations can also be detected in cancers, and hence mutations in these genes should be regarded as either somatic or germline in origin.

Disease-Defining molecular alterations

While rare, a few recurrent gene rearrangements define rare subtypes of invasive breast carcinoma. The *ETV6-NTRK3* fusion is associated with secretory breast carcinoma [1,2], and the *MYB-NFIB* fusion is associated with adenoid cystic carcinoma [3]; each accounts for less than 1% of invasive carcinomas. Loss of expression of the cell adhesion molecule cadherin 1 (CDH1) is observed in almost all invasive lobular carcinomas as well as some carcinomas with mixed ductal and lobular histologic features [4]. *CDH1* mutations are usually truncating and most frequently co-occur with heterozygous loss of 16q (either by deletion or copy neutral LOH) to induce complete loss of CDH1 expression. While the mechanisms for loss of CDH1 expression are heterogeneous, comprehensive genomic profiling of lobular carcinomas has shown inactivation of *CDH1* in virtually all cases [5]. Loss of *CDH1* function is clinically relevant not only for diagnosis but also for patient management, since germline *CDH1* mutations are associated with a hereditary predisposition to breast and gastric cancers with a characteristic infiltrating growth pattern and characteristic “signet ring” cells [6]. Other than the two recurrent gene fusions and *CDH1* mutations associated with loss of protein expression, genetic abnormalities in breast cancer are not specific for a particular histopathologic diagnosis. The spectrum of mutations does vary in frequency across histologic subtypes, however. *TP53* mutations are especially common in medullary carcinomas and triple negative carcinomas, and *GATA3* mutations are more common in mucinous carcinomas [7]. In addition to *CDH1* mutations, lobular carcinomas are enriched for *PTEN* mutations, which are mutually exclusive with *PIK3CA* mutations; additionally, *FOXA1* mutations are more frequent and *GATA3* mutations are less frequent in lobular carcinomas, suggesting differences in estrogen pathway modulation between lobular carcinomas and ductal carcinomas [5]. Frequent expression of FOXA1 and GATA3 in breast cancer also makes these markers helpful in the diagnostic workup of breast cancer [5]. Lobular carcinomas also more frequently harbor *ERBB2* and *ERBB3* sequence variants [8]. Aside from a close association with loss of CDH1 expression, however, there are no specific genomic aberrations that are diagnostic of lobular carcinoma.

Clinical molecular subtypes

Three biomarkers are an essential part of the diagnostic workup and clinical management of breast cancer: estrogen receptor alpha (ER-α), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/neu, commonly referred to as HER2). Expression of ER, PR, and HER2 is measured by immunohistochemistry (IHC). In situ hybridization (ISH) is also used to determine HER2 status by the presence or absence of *ERBB2* (*HER2*) gene amplification, since *ERBB2* amplification is very closely correlated with HER2 overexpression [9]. In the United States, evaluation of biomarkers is performed either according to FDA approved criteria or according to current guidelines published by the American Society of Clinical Oncology and the College of American Pathologists (Table 2) [10,11]. Diagnostic evaluation of breast cancer specimens includes the determination of histologic subtypes, tumor grade, and stage, as well as an evaluation of hormone receptor status and HER2 status; a mitotic index or evaluation of Ki-67 is typically also performed as a marker of proliferation. The majority of breast cancers express estrogen and progesterone receptors,

Table 2
Clinical Molecular Subtypes of Breast Cancer.

Clinical molecular subtype	Estrogen receptor IHC [10]	Progesterone receptor IHC [10]	HER2 IHC [11]	HER2 ISH [11]
Hormone receptor positive, HER2 negative	≥1% positive nuclear staining (1–10% nuclear staining is considered “low positive”) [10]	Any staining pattern	Negative (0 or 1+) or equivocal (2+) staining with negative ISH	HER2/centromere ratio <2.0 and HER2/cell <4.0 (Group 5) or equivocal (2+) IHC staining with negative IHC-guided ISH score in Groups 2, 4, or 5
HER2 positive	Any staining pattern	Any staining pattern	Positive (3+) or equivocal (2+) staining with positive ISH	HER2/centromere ratio ≥2.0 and HER2/cell ≥4.0 (Group 1) or equivocal (2+) reflex IHC staining with ISH score in Groups 1 or 3
Triple negative	<1% positive nuclear staining	<1% positive nuclear staining	Negative (0 or 1+) or equivocal (2+) staining with negative ISH	HER2/centromere ratio <2.0 and HER2/cell <4.0 (Group 5) or equivocal (2+) IHC staining with negative IHC-guided ISH score in Groups 2, 4, or 5

and 15–20% of breast cancers overexpress HER2 on the cell membrane, while a minority (15–20%) lack expression of estrogen receptors, progesterone receptors, or HER2 receptors and are called "triple negative." Triple negative breast cancer is currently a very active area for research and drug development. Breast cancers that lack expression of ER, PR, or HER2 (and/or: lack *ERBB2* amplification) are quite heterogeneous in terms of their expression profile and their genomic signatures [12]. Triple negative breast cancers have the worst overall prognosis, but the genomic profiles of this subgroup are quite heterogeneous at the DNA level and represent a mix of tumors with good and poor prognoses.

Intrinsic molecular subtypes

In 2000, Perou and colleagues published their seminal study on the hierarchical clustering of differential expression levels for over 1700 genes in breast cancer; this study established five intrinsic subtypes of breast cancer (luminal A, luminal B, HER2 enriched, basal like, and normal like) [13]. Perou's five intrinsic subtypes were based on expression levels of genes associated with cellular proliferation, basal vs. luminal epithelium, estrogen responsiveness, and HER2 activation. The "normal" pattern described by Perou has since been challenged as a potential artifact of inadequate tumor enrichment, and most researchers now accept four intrinsic subtypes of breast cancer: Luminal A, Luminal B, HER2-enriched, and Basal-like [14]. More recently, Perou and others have described a "claudin low" subtype with low expression of proliferation markers and high expression of genes involves in the immune system response and multiple other gene families [15-17]. Perou's intrinsic subtypes have been reproduced in numerous subsequent genomic studies on breast cancer and remain a core conceptual framework for the genomic classification of breast cancers [18,19].

Hormone receptor expression most likely precedes and promotes carcinogenesis in luminal cells of the breast [20]. Expression of hormone receptors and responsiveness to hormone therapy in breast cancers evolve with treatment, and secondary resistance mutations in *ESR1* are common [21-23]. Recent large genomic studies have confirmed that hormone receptor positive tumors correlate well (but not perfectly) with the luminal intrinsic subtypes [18,19]. Rare breast cancers with *ESR1* (ERα) expression can show a basal rather than a luminal molecular subtype due to aberrant expression of an alternatively spliced form referred to as EΔ7. This form of ERα is missing exon 7 and has a dominant negative function in repressing ERα-responsive genes [24].

Like hormone receptor expression, HER2 expression may precede and promote carcinogenesis. Most but not all breast cancers with HER2 overexpression show evidence of *ERBB2* (*HER2*) gene amplification. Rare activating mutations also occur and can be targeted with small molecule inhibitors (lapatinib, afatinib, and others) [25]. Tumors with a HER2 positive clinical molecular subtype are a mix of HER2 enriched and luminal intrinsic subtypes; the latter are typically "Luminal B" and characterized by a higher proliferation index.

Basal like breast cancers are defined by expression of basal keratins and low or absent expression of luminal keratins. This subgroup has been found to be heterogeneous at the molecular level and includes the aforementioned "claudin low" subtype. All are characterized by minimal or absent expression of genes associated with estrogen responsiveness, and minimal or absent expression of HER2; the associated clinical molecular subtype is most often triple negative.

Genomic profiling of RNA expression in the clinical setting

A number of RNA-based genomic assays are clinically approved for disease stratification in patients with ER-positive, HER2-negative disease. These assays were designed to generate a score reflecting the risk for recurrent disease based on the overall expression profile observed in a breast cancer sample, resulting in better prognostic stratification for these patients, and aiding therapeutic decisions. Commonly referred to as "genomic assays," these RNA expression assays determine the relative expression of luminal and basal keratins, proliferation markers, HER2 and associated genes, genes involved in hormone signaling, and genes associated with the immune response, together presenting an overall picture of the activated gene pathways and the proliferation rate of a cancer. Oncotype DX® is the most frequent assay performed in the United States (Genomic Health, Redwood City, California), and it has been endorsed by several professional organizations including the American Joint Committee on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN). The TAILORx trial included long term follow up of patients whose tumors were tested by Oncotype DX, and confirmed a low risk of recurrence for most patients with an intermediate or low risk score, particularly for older patients without additional clinical risk factors [26,27]. The MammaPrint assay was developed before Oncotype DX and is widely used in European countries; testing is offered by Agendia (Amsterdam, The Netherlands). The MINDACT trial demonstrated the prognostic utility of the MammaPrint assay [28,29], and this assay is endorsed by multiple professional organizations in Europe and the United States. The MammaPrint assay was clinically validated for patients with either node negative or node positive disease. The Oncotype DX assay was originally validated for breast cancer patients with node negative disease as part of the National Surgical Adjuvant Breast and Bowel Project (NSABP B-14 and B-20) [27,30,31], but Oncotype DX can also stratify risk in patients with node positive disease, as demonstrated by the Southwest Oncology Group (SWOG) [32,33]. A third gene expression assay is Prosigna, previously known as the PAM50 assay; this is licensed to independent CLIA-certified laboratories by Nanostring (Seattle, Washington). The Prosigna assay generates a risk of recurrence score, but it is also useful for intrinsic molecular subtyping [14]. The BluePrint assay from Agendia works similarly to generate an intrinsic subtype (Luminal-type, HER2-type, or Basal-type) using gene expression profiling. Additional RNA expression profiling assays include the EndoPredict assay [34,35] and the Breast Cancer Index [36-39], both of which are used to generate a risk of recurrence similar to the aforementioned assays. Immunohistochemical markers are also useful for predicting prognosis in breast cancer. Beyond the clinical molecular subtypes, quantification of immunohistochemical staining and other protein expression assays can generate prognostic information; the most common of these are the IHC4 assay [40] and the Magee Equation recurrence score using combined quantitative information from ER, PR. HER2, and Ki-67 immunohistochemistry [41,42]. Another expression assay that is performed on the protein level is measurement of levels of urokinase-type plasminogen activator (uPA)/plasminogen activator inhibitor-1 (PAI-1) by using an enzyme-linked immunosorbent assay (ELISA) [43]. The uPA/PAI-1 method is fairly inexpensive and simple to perform, and it has been endorsed and employed mainly in European countries to identify breast cancer patients at an elevated risk for recurrence, similar to RNA expression assays. While extended clinical use of gene profiling assays is advocated for by some, genomic expression profiling does not always provide helpful or accurate information beyond the intended use of the assay [44], and the clinical value of genomic assays appears to be quite limited for those breast cancers with low grade histopathology and unequivocal biomarker status [41]. A list of clinically approved genomic RNA expression profiling assays is shown in Table 3.

Table 3
Assays Used to Predict Risk of Recurrence in Hormone Receptor Positive, HER2 Negative Breast Cancer.

Assay	Manufacturer	AJCC Evidence Level	Eligible Tumor Type(s)	Description
Oncotype DX®	Genomic Health	1	Node negative	21-gene assay categorizes cancers as low, intermediate, or high risk
MammaPrint	Agendia	2	Node negative or positive < 5 cm	70-gene assay, low or high risk
Prosigna® PAM50	Nanostring	2	Node negative, tamoxifen treated	50-gene assay, low or high risk
EndoPredict®	Myriad Genetics	2	Node negative or positive (1–3 nodes), pre- or postmenopausal	8-gene assay combined with tumor size and nodal status to assign risk score; low or high risk
Breast Cancer Index	Biotheranostics	2	Node negative, untreated or tamoxifen treated	2-gene assay generates H/I index associated with low or high risk

Evidence levels for different RNA based gene expression assays assigned by the American Joint Committee on Cancer. Part XI: Chapter 48, Breast. In: M.B. Amin et al. (eds.), AJCC Cancer Staging Manual, Eighth Edition, American College of Surgeons, Chicago, IL, USA.

Genomic profiling of copy number alterations (CNAs) and loss of heterozygosity (LOH)

Early genetic studies on breast cancer employed karyotyping, FISH, flow cytometry, and comparative genomic hybridization (CGH) testing to describe recurrent chromosomal abnormalities. Such studies established many recurrent genomic abnormalities in breast cancer, including frequent hyperdiploidy [45-47], polyclonality [48-53], and gene amplification including *ERBB2* [9,54-56] and/or *MYC* [56-58]. The latter abnormality, amplification, could be observed in homogenously staining regions of chromosomes in karyotype preparations of G-banded metaphase cell preparations [59-61]. Perhaps due to differences in short term and long term cytogenetic culture preparations [50], and perhaps also due to a limited number of samples studied, early studies yielded different and sometimes conflicting information on recurrent copy number alterations (CNAs) in breast cancer [53,62,63]. Array CGH technology allowed for the study of breast cancer genomics without the requirement for cell culture [62-68]. Clear patterns emerged regarding the prognostic implications of CNAs in breast cancer. Early array CGH studies also established an important link between gene amplification and overexpression [69].

Two large genomic studies published in 2012 yielded a wealth of information on the landscape of copy number alterations and allelic imbalances in breast cancer [18,19]. These studies demonstrated many of the recurrent copy number abnormalities that had been previously described, including gains of 1q, 8q, and 17q and losses of 8p, 16q, and 17p. Both studies included long term clinical follow up and in depth molecular characterization of primary breast cancers; but the two studies grouped copy number alterations differently based on the combined evidence from multiple genomic platforms. The Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) study described ten integrative clusters weighted more toward recurrent DNA copy number profiles [19]; and The Cancer Genome Atlas Network (TCGA) described five integrated subtypes weighted more toward RNA expression profiles [18]. In both studies, the genomic copy number groups shared similar common alterations among subtypes, suggesting limited specificity and perhaps limited clinical utility of genome wide copy number / LOH profiles. However, a follow up study from the METABRIC dataset has confirmed several important prognostic biomarkers in the copy number landscape: amplicons on 8p12, 8q24, 11q13, and 17q23 [70]. All are associated with an increased risk of late relapse (recurrence of disease up to decades after the initial diagnosis) in women diagnosed with ER positive, HER2 negative breast cancers [70]. Most individual copy number alterations of clinical significance in breast cancer are adverse prognostic indicators; these include amplification of 8p11.2 [71], 8q24 [57,58], 17q23 [72-74], and 20q [75,76], and deletion or loss of heterozygosity (LOH) of 10q23 (including *PTEN*) and 17p (including *TP53*). Recently, amplification of a genomic region on 9p24.1 including *JAK2, CD274* (PD-L1 gene), and *PDCD1LG2* (PD-L2 gene) has been identified in 1–2% of breast cancers [77]. 9p24.1 amplification is more common in triple negative breast cancers and has been associated with responsiveness to immunotherapy and JAK2 inhibition in this tumor type [77]. In addition to providing prognostic and predictive information, genomic copy number profiling can also identify recurrent patterns associated with histologic subtypes of breast cancer. Simple or nearly normal copy number profiles are characteristic of tubular carcinoma, adenoid cystic carcinoma, mucinous carcinoma, and carcinoma with neuroendocrine features [78]. Very complex copy number profiles with “firestorm” or “sawtooth” patterns are typical of medullary carcinoma, metaplastic carcinoma, and invasive micropapillary carcinoma [78]. Table 4 summarizes the recurrent clinically relevant copy number changes and regions of LOH seen in breast cancer.

Comprehensive genomic testing modalities for somatic variant detection can identify copy number changes in genes associated with increased hereditary breast cancer risk [79]. Therefore, it is important to evaluate for the possibility of a germline alteration when a deletion or other potentially inactivating structural rearrangement is detected in one of these genes (Table 5).

Sequence alterations

Pathogenic sequence alterations in DNA samples from primary breast cancers occur most commonly in *PIK3CA, GATA3*, and *TP53*; other genes are individually mutated in less than 10% of breast cancers overall [18]. Genes commonly affected by copy number alterations or LOH in breast cancer can alternatively harbor point mutations or other forms of sequence variation (including small insertion-deletion mutations). Certain genes are correlated with histologic or molecular subtypes of breast cancer (for example, *CDH1* mutations in lobular carcinomas [4,6,80,81]). Inactivating mutations in genes associated with hereditary breast and ovarian cancer syndromes should prompt consideration of a germline mutation, and genetic counseling can be very helpful in this context for guiding follow up constitutional genetic testing for the patient and potentially affected family members [82,83]. Germline mutations associated with a hereditary risk for breast cancer are generally autosomal dominant with reduced penetrance; thus, not all individuals carrying a pathogenic germline mutation will develop cancer. The potential for a hereditary risk varies based on the specific alteration. *TP53* mutations are among the most common sequence alterations in breast cancer and are usually somatic rather than inherited [84]. Mutations in *BRCA1* or *BRCA2*, however, are fairly uncommon, and so these should generally raise clinical suspicion of a hereditary cancer predisposition (Table 5). Often, the initial mutational event in a tumor suppressor gene (either germline or somatic) is a sequence alteration, and the “second hit” causing loss of tumor suppressor function is a large deletion or LOH event [79].

Table 4
Clinically significant copy number alterations in breast cancer.

Alteration	Relevant Gene(s)	CGC Evidence Level	Subgroup Association(s)
1q gain	unknown	2	Most common copy number alteration, often with 16q loss; all subtypes
8p11.2 amplification	*FGFR1, ZNF703*	2	METABRIC IntClust6, ER positive
8q24 amplification	*MYC*	2	METABRIC IntClust9, ER positive
9p24 amplification	*JAK2, CD274, PDCD1LG2*	2	Enriched in TNBC
10q23.3 loss or LOH	*PTEN*	2	Enriched in TNBC and in lobular carcinoma
11q13-q14 gain / amplification	*CCND1, EMS1*, and others	2	METABRIC IntClust2
16q loss / LOH	*CDH1*	2	METABRIC IntClust2, ER positive
17p loss / LOH	*TP53*	2	TNBC, basal-like intrinsic subtype
17q12 amplification	*ERBB2* (*HER2*)	1	METABRIC IntClust5, HER2-enriched
17q21 amplification	*TOP2A*	2	METABRIC IntClust5, HER2-enriched
17q23 amplification ("17q distal amplicon")	*RPS6KB*, others	2	METABRIC IntClust1
19q12	*CCNE1*	2	METABRIC IntClust5; HER2-enriched
20q gain; 20q13 amp	*AURKA, GNAS, ZNF217*	2	METABRIC IntClust1, ER Positive

Table 5
Genes with known hereditary risk associations in breast cancer.

Gene	Associated Syndrome; Breast Cancer Subtype
ATM	Ataxia telangiectasia syndrome
BARD1	TNBC
BRCA1	BRCA-Related Breast/ Ovarian Cancer Syndrome; TNBC
BRCA2	BRCA-Related Breast/ Ovarian Cancer Syndrome; TNBC
CDH1	Hereditary Diffuse Gastric Cancer and Lobular Breast Cancer
CHEK2	Inherited breast cancer
NBN	Nijmegen Breakage Syndrome
NF1	Neurofibromatosis type 1
PALB2	Fanconi anemia
PTEN	Cowden syndrome
RAD51C	TNBC
RAD51D	TNBC
STK11	Peutz-Jeghers syndrome
TP53	Li-Fraumeni syndrome

Somatic genomic testing based on DNA sequencing, such as large NGS cancer panels, is not usually performed for surgically resectable breast cancer. In the setting of unresectable, metastatic, or recurrent disease, however, genomic sequencing tests can be very useful for identifying targetable abnormalities. A recent study demonstrated that *PIK3CA* mutations respond to targeted therapy in advanced hormone receptor positive, HER2 negative breast cancers [85]. Large sequencing panels can identify gene mutations that are individually rare but potentially targetable, including *ERBB2* and other ERBB family members (*EGFR, ERBB3*, and *ERBB4*) [25,86,87], and other kinase genes.

Sequence alterations associated with therapy resistance commonly emerge in the setting of residual or recurrent disease. *ESR1* mutations are frequent in breast cancer patients treated with hormone therapy [22,88] and can be detected in circulating cell free DNA, also called "liquid biopsy" [89-92]. Liquid biopsy is increasingly used in the clinical setting to detect subclonal resistance mutations in *ESR1*. Likewise, resistance mutations in ERBB gene family members (*EGFR, ERBB2*/*HER2, ERBB3, ERBB4*) can occur after exposure to HER2-targeted therapy [93]; *HER2* kinase domain mutations are a recurrent abnormality in this setting [94]. A list of genes associated with clinically significant sequence alterations in breast cancer is shown in Table 6.

Gene fusions and oncogene activation by structural rearrangements

Recurrent gene fusions in cancer include the *ETV6-NTRK3* rearrangement associated with secretory breast cancer [1,2] and *MYB-NFIB* rearrangement associated with adenoid cystic carcinoma [3]. These along with another rare fusion, *MECT1-MAML2* [95], are associated with origin in adnexal structures of the breast that phenotypically resemble salivary gland epithelium.

Rare rearrangements involving kinase genes are highly targetable. The *MAGI3-AKT3* fusion is a recurrent event that is targetable by AKT small molecule inhibitors [86]. Fusions involving *RET, FGFR1*, and *FGFR2* have also been identified in breast cancer and are highly targetable [96-98]. *NTRK* inhibitors are FDA approved for advanced or metastatic tumors harboring NTRK gene fusions regardless of tumor type. Routine genomic profiling including fusion detection in breast cancer is likely to identify more targetable rearrangements in the future.

While most clinically important rearrangements are activating, rearrangements that impair or inactivate genes can also be clinically significant. Rearrangements involving the ligand binding domain of *ESR1* have been identified in hormone resistant breast cancers, some of which also harbored *ESR1* resistance mutations [21]. Functionally inactivating rearrangements of tumor suppressor genes are a recurrent abnormality in all cancers, and these can occasionally represent a germline alteration.

Other rearrangements appear frequently in breast cancer but have no definitive clinical significance. Rearrangements of neuregulin 1 (*NRG1*) are a recurrent finding in breast cancers [99,100] and are frequently found in cases with 8p11-p12 amplification [71]. *NRG1* fusions have been associated with an oncogenic transcriptional isoform called gamma-heregulin [101], but the clinical significance of *NRG1* rearrangement remains for the most part unclear aside from its possible use as a marker of poor prognosis [102].

Genomic signatures of defective DNA repair

Genomic signatures are hallmark patterns of mutations that are not specific to a particular genomic region but rather are observed anywhere in the genome. Several different genomic signatures have been identified in breast and other cancers. Chromothripsis, or "chromosome shattering," can occur during cancer development, leaving a signature pattern of alternating gains and losses (typically alternating between two or maybe three different copy states) in the affected chromosome regions [103]. Chromothripsis is theorized to result from damage occurring when one or more chromosomes or chromosome regions are retained within micronuclei [103]. Another pattern of DNA damage is kataegis, or a "thunderstorm" composed of clustered mutations in a region of the genome. Kataegis has been attributed to abnormal activity of the apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) family of cytidine deaminases and is characterized by $C>T$ or $C>G$ substitutions, typically within TpCpN trinucleotides

Table 6
Major clinically significant genes associated with somatic sequence alterations in breast cancer.

Gene(s)	CGC Evidence Level	Clinical Significance and Subgroup Association(s)	Therapy Implication(s)
AKT1	2	Metastatic BC	AKT inhibitors
ATM	1	Possible hereditary risk; TNBC	PARP inhibitors (germline)
BRCA1, BRCA2	1	Often hereditary risk; TNBC	Platinum based therapy; PARP inhibitors (germline)
CBFB	2	ER-positive, Metastatic BC	
*CCND1, CCNE1**	2	HER2-enriched	CDK4/6 inhibitors
*CDK4, CDK6**	2	ER-positive, Metastatic BC	CDK4/6 inhibitors
CDH1	1	Lobular histology; Possible hereditary risk	
CDKN2A	2	Metastatic BC	
CHEK2	1	Often hereditary risk	PARP inhibitors (germline)
*ERBB2**	1	Rare activating sequence alterations; kinase domain resistance mutations; HER2-enriched	HER2-targeted therapy
ESR1	1	Metastatic ER-positive	Hormone therapy resistance
FGFR1-4	2	ER-positive	FGFR inhibitors
FOXA1	2	ER-positive, Luminal subtype, lobular histology	
GATA3	2	ER-positive, Luminal subtype	
*JAK2**	2	TNBC	JAK2 inhibitors, immunotherapy
MAP2K4	2	Metastatic BC	
MAP3K1	2	ER-positive, Metastatic BC	
*MYC**	2		
NBN	1	Possible hereditary risk	PARP inhibitors (germline)
NF1	1	Possible hereditary risk	mTOR/PI3K/AKT inhibitors (germline)
NTRK1-3	1		NTRK inhibitors
PALB2	1	Often hereditary risk	PARP inhibitors (germline)
PIK3CA	1	ER-Positive, Luminal subtype	PI3K inhibitors for selected hotspot mutations; acquired hormone resistance
PTEN	2	Loss in lobular BC; Possible hereditary risk	mTOR/PI3K/AKT inhibitors; radiation contraindicated
RB1	2	Metastatic BC	Acquired hormone resistance
STK11	1	Possible hereditary risk	
TBX3	2	Lobular BC	
*TOP2A**	2		Anthracycline inhibitors
TP53	1	TNBC, HER2-enriched, Metastatic BC Possible hereditary risk	Radiation contraindicated

* Indicates genes more commonly activated by amplification than by sequence variationBC, breast cancer. TNBC, triple negative breast cancer.

[104]. Several recurrent patterns of genomic mutation, termed "Signature 2" and "Signature 13," are characterized by kataegis related to APOBEC dysfunction in breast cancer [104]. Another genomic signature has been termed a "firestorm," and like chromothripsis, this signature affects a localized area of the genome. Unlike chromothripsis, a firestorm shows very high level amplification (up to 30 copies or more) of a very narrow genomic region that is copied many times over in a particular region of the genome [105]. A firestorm is thought to result from cyclic breakage-fusion-bridge DNA repair events occurring early in cancer development 105,106]. The firestorm pattern of DNA amplification is seen most commonly in Luminal B and HER2 enriched breast cancers and has been associated with a poor prognosis [105,107]. The genes *ERBB2* (*HER2*) and *CCND1* are frequently amplified in these so called "firestorms" on single nucleotide polymorphism (SNP) array testing.

Some genomic signatures are currently used as biomarkers to identify patients for certain targeted therapies. *BRCA1/2*-deficient tumors can show a characteristic pattern of DNA damage called "Signature 3" [104,108]. On SNP array, *BRCA1/2*-deficient tumors frequently show a pattern of numerous large scale transitions in copy number and allelic imbalance or loss of heterozygosity (LOH), the latter including telomeric allelic imbalance, throughout the genome [109-111]. These *BRCA1/2*-deficient patterns result from deficient homologous recombination at double strand DNA breaks, resulting in abnormal non-homologous end joining. Termed homologous recombination deficiency or HRD, this genomic signature (also referred to as a "sawtooth pattern" [105] or "genomic scar" [110,111]) is a useful predictor of responsiveness to PARP inhibitors and platinum based chemotherapy agents (cisplatin, carboplatin) [110-112]. The same signature, when observed in triple negative breast cancers lacking a detectable pathogenic germline alteration in *BRCA1* or *BRCA2*, likewise appears to be a useful predictor of responsiveness to PARP inhibitors and platinum based chemotherapy [112-115]. Another related pattern predicting responsiveness to platinum based chemotherapy is the tandem duplicator phenotype [116]. This pattern of duplications is found in triple negative breast cancers with loss of both *BRCA1* and *TP53* function and is thought to be a mechanism by which such tumors acquire pathogenic alterations in tumor suppressor genes and oncogenes [116]. Sequencing shows microhomologies at the breakpoints of tandem duplications attributable to microhomology-mediated breakage induced repair. There is a bimodal size distribution of these tandem duplications with peaks at ~10 kb and ~150 kb [116]. These tandem duplications are challenging to detect with currently available SNP array

platforms that are typically designed to detect copy number alterations on a scale of 200 kb or larger [117].

Some patterns of mutation are infrequent in breast cancer but are highly significant if identified, due to the availability of targeted therapy. Mismatch repair deficiency (MMRd) or microsatellite instability (MSI), is associated with "Signature 6" [104] and a high tumor mutation burden (TMB). Breast cancers with MMRd/MSI-high status are fairly rare and typically involve somatic rather than germline mutations in MMR genes, although germline mutations have also been observed in breast cancer [118]. Due to tumor-agnostic approval by the FDA for this class of molecular alteration, these breast cancers are targetable with the immune checkpoint inhibitor pembrolizumab (Keytruda). New markers predicting responsiveness to immunotherapy are emerging, including an amplicon on 9p24.1 containing *JAK2* and the genes encoding PD-L1 and PD-L2; preliminary evidence suggests that this is an important biomarker for responsiveness to immunotherapy in a small fraction (1–2%) of breast cancers, especially triple negative breast cancers [77]. Outside of genomic profiling for advanced or metastatic breast cancers, measurement of tumor infiltrating lymphocytes (TILs) and immunohistochemical evaluation of PD-L1 expression are clinically used to identify candidates for immunotherapy.

Emerging genomic biomarkers: miRNAs, methylation, and beyond

Large genomic studies have shown differential expression of miRNAs that are recurrent in breast cancer [18]. Certain miRNA expression patterns have been associated with *TP53* mutation [18] or *PTEN* mutation [119] and are associated with poor prognosis. Likewise, global patterns of hypermethylation or hypomethylation have been identified in breast cancer [18]. The hypermethylated pattern affects CpG islands in gene promoter regions and has been associated with the Luminal B expression subtype; the hypomethylated pattern is seen primarily in the basal-like expression subtype [120]. Overall patterns observed on methylation profiling have also provided insights on breast cancer development [121]. In addition to global methylation patterns, hypermethylation is an important mechanism for inactivation of tumor suppressor genes, including *BRCA1* [114].

Conclusions

A major reason that genomic profiling has not been widely adopted in the diagnostic workup of breast cancer is that these assays have not been completely standardized to permit platform-agnostic correlation with patient outcomes. Furthermore, genomic assays are more challenging to interpret in clinical specimens containing not only invasive tumor but also non-tumor cells and non-invasive (in situ) cancer precursors; in contrast, clinically available IHC and ISH assays allow cell by cell interpretation of abnormalities in selected cell populations. Furthermore, both polyploidy and polyclonality can confound the interpretation of genomic abnormalities, including the degree of copy number and allelic imbalances. Despite these substantial challenges, many genomic RNA expression assays are routinely employed to aid clinical decision making, and DNA-based genomic assays are routinely used in patients with recurrent, progressive, non-resectable, or metastatic disease. Adoption of routine genomic testing for all invasive breast cancers will require standardization across platforms and professional guidelines for application and interpretation of genomic sequence and copy number data. Given the increasing availability of therapies based on genomic signatures and rare but highly targetable genetic abnormalities, the clinical utility of genomic profiling for breast cancer is evident. Routine use of genomic testing may facilitate patient management and contain costs by personalizing breast cancer treatment. The immediate task for clinical laboratories is the development of technical standards to guide broader use of genomic profiling in breast cancer.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2020.02.002.

CRediT authorship contribution statement

Katherine B. Geiersbach: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing. **Hui Chen:** Methodology, Investigation, Writing - review & editing. **Rajyasree Emmadi:** Methodology, Investigation, Writing - review & editing. **Gloria T. Haskell:** Methodology, Investigation, Writing - original draft, Writing - review & editing. **Xinyan Lu:** Methodology, Investigation, Writing - review & editing. **Yajuan J. Liu:** Methodology, Investigation, Writing - review & editing. **Karen Swisshelm:** Methodology, Investigation, Writing - review & editing.

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