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Genomic profiling of breast cancers

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Abstract

Purpose of review—To describe recent advances in the application of advanced genomic technologies towards the identification of biomarkers of prognosis and treatment response in breast cancer.

Recent findings—Advances in high-throughput genomic profiling such as massively parallel sequencing have enabled researchers to catalogue the spectrum of somatic alterations in breast cancers. These tools also hold promise for precision medicine through accurate patient prognostication, stratification, and the dynamic monitoring of treatment response. For example, recent efforts have defined robust molecular subgroups of breast cancer and novel subtype-specific oncogenes. In addition, previously unappreciated activating mutations in human epidermal growth factor receptor 2 have been reported, suggesting new therapeutic opportunities. Genomic profiling of cell-free tumor DNA and circulating tumor cells has been used to monitor disease burden and the emergence of resistance, and such 'liquid biopsy' approaches may facilitate the early, noninvasive detection of aggressive disease. Finally, single-cell genomics is coming of age and will contribute to an understanding of breast cancer evolutionary dynamics.

Summary—Here, we highlight recent studies that employ high-throughput genomic technologies in an effort to elucidate breast cancer biology, discover new therapeutic targets, improve prognostication and stratification, and discuss the implications for precision cancer medicine.

Keywords

breast cancer; genomics; heterogeneity; molecular subtype; somatic alteration

INTRODUCTION

Breast cancer is the leading cause of cancer death among women worldwide and is comprised of a group of heterogeneous diseases that differ significantly in their molecular and clinical characteristics. Such interindividual variability complicates the clinical management of the disease, as well as the characterization of breast cancer biology, but is

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only partially explained by traditional clinicopathological factors such as age, stage, histological grade, and estrogen receptor (ER) status. Recurrent somatic alterations have been reported at the mutational and copy number levels, the most notable being *ERBB2* amplification, which is present in 15% of cases, and represents the first successful therapeutic target defined by a genomic aberration [1,2]. Recent years have heralded significant progress in delineating the genomic diversity of breast cancer as a result of technological advances in high-throughput genomics, including massively parallel sequencing (MPS). Such approaches have enabled an in-depth characterization of the landscape of somatic alterations in breast cancer, including mutations, structural aberrations, copy number aberrations, transcriptional changes, and epigenetic modifications [3,4■,5–10]. The integration of genomic and transcriptional profiles led to the identification of novel breast cancer subgroups with distinct clinical outcomes, resulting in a robust molecular taxonomy, which refines the existing classification schemes [4■]. These comprehensive genomic profiling studies suggest new avenues for molecularly targeted therapy and improved patient stratification. As discussed below, genomic techniques are also being exploited to enable more accurate prognostication, and the real-time monitoring of treatment response and minimal residual disease towards the goal of precision cancer care.

BREAST CANCER GENOMIC LANDSCAPES

The advent of high-throughput genomic technologies has led to rapid advances in our understanding of the genomic, epigenomic, transcriptomic, and proteomic changes that underlie breast cancer pathobiology. In recent years, a number of comprehensive genomic profiling studies have characterized the spectrum of somatic aberrations and the genomic heterogeneity of breast cancer [3,9,10]. For example, Stephens *et al.* [9] leveraged MPS to analyze 100 tumors at the whole exome and copy number levels, and identified nine novel candidate driver genes (*AKT2*, *ARIDIB*, *CASP8*, *CDKN1B*, *MAP3K1*, *MAP3K13*, *NCOR1*, *SMARCD1*, and *TBX3*). Banerji *et al.* [3] confirmed a number of known mutations (*PIK3CA*, *TP53*, *AKT1*, *GATA3*, and *MAP3K1*) in addition to novel mutations in the gene encoding the CBFB transcription factor and deletions of its partner *RUNX1*. This study also identified recurrent *MAGI3–AKT3* fusions in triple-negative [ER/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2)-negative] breast cancers (TNBCs), resulting in constitutively active AKT kinase signaling, which could be targeted by a small molecule inhibitor [3]. Nik-Zainal *et al.* [6,7] characterized 21 primary breast cancers via whole genome sequencing (WGS) and employed the genomic data to infer mutational processes and tumor evolutionary histories. In a study of ER-positive breast cancer, Ellis *et al.* performed WGS of 46 tumor/normal pairs and whole exome sequencing (WES) of 31 cases from patients in two neo-adjuvant aromatase inhibitor trials to elucidate biomarkers of response. In addition to identifying recurrent mutations in novel genes such as *TBX3*, *RUNX1*, *LDLRAP1*, *MYH9*, *AGTR2*, *STMN2*, *SF3B1*, and *CBFB*, they find that *GATA3* mutations correlated with a treatment-induced antiproliferative effect.

Various studies sought to incorporate multiple molecular readouts to delineate mechanisms of disease biology. For example, Shah *et al.* [8] analyzed 104 TNBCs through a combination of WES, WGS, RNA sequencing, and array-based copy number profiling. They report a diverse spectrum of clonal mutational frequencies with dominant subclones composed of a

handful of driver mutations and with basal-like tumors exhibiting greater variation than nonbasal TNBC [8]. The Cancer Genome Atlas performed a comprehensive analysis of multiple 'omic' (copy number, mutational, DNA methylation, transcriptome, and proteome) readouts with approximately 450 samples profiled on all five platforms to identify four major heterogeneous subgroupings, and confirm high frequency (>10% overall) somatic mutations in a handful of genes (*TP53*, *PIK3CA*, and *GATA4*), whereas the vast majority of mutations occur in a small (1–3%) proportion of cases [10]. In the largest breast cancer cohort described to date, Curtis *et al.* [4■] performed an integrated analysis of genome-wide copy number and transcriptional profiles in a discovery set of nearly 1000 primary tumors from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) cohort with long-term clinical follow-up, revealing 10 molecular subgroups with distinct clinical outcomes, which they subsequently validate in an additional series of approximately 1000 cases. The majority of subgroups demonstrated enrichment for a number of putative driver genes, and rare, but recurrent, copy number alterations were found in a number of therapeutic targets such as amplification of *IGF1R*, *KRAS*, and *EGFR*. Deletions in *MAP3K1* and *MAP2K4* were also noted in-line with inactivating mutations reported in other studies [5,9].

Importantly, a recent meta-analysis of these and other breast cancer sequencing studies identified a subset of HER2 amplification-negative patients with activating mutations in the kinase and juxtamembrane domains of HER2, revealing an alternate mechanism of pathway activation for this well characterized oncogene [11■■]. Although such HER2-mutant breast cancers are relatively rare, these patients may benefit from existing anti-HER2 targeted therapies, such as the tyrosine kinase inhibitor, neratinib, and this will be explored in a prospective trial. This finding highlights the role of unbiased discovery approaches such as WES/WGS and the integration of multiple genomic views in the interpretation of breast cancer biology.

Cancer genome sequencing studies have also revealed defects in chromatin regulatory machinery, including multiple subunits of the mSWI/SNF (BAF) complex in numerous cancers [12–14]. For example, *ARID1A* is mutated in approximately 5% of breast cancers and more frequently in endometrial, clear cell renal, and ovarian cancer. Moreover, in some tumor types, *ARID1A* mutations may have prognostic utility [15]. These findings point to the importance of epigenomic alterations in tumor progression, and new studies have highlighted the complex interplay between the genome and epigenome. A recent study by Vire′ *et al.* [16■] shows that EMSY functions as a luminal B oncogene that is recruited to the miR-31 promoter by ETS-1, where it interacts with the H3K4 demethylase, JARID1B, torepress transcription of the antimetastatic micro RNA *miR-31*. Yamamoto *et al.* [17■] evaluated the impact of somatic alterations in the *JARID1B* gene, which is amplified and overexpressed in luminal breast cancers and mutated in basal-like tumors. Through elegant genomic and functional assays, they characterize JARID1B as a luminal lineage-specific oncogene associated with poor prognosis [17■].

TOWARDS ROBUST MOLECULAR SUBTYPING

The above findings emphasize what has been appreciated for some time, namely that breast cancer is not a single entity, but a complex and heterogeneous group of diseases with distinct biological and clinical features. A key premise of precision medicine is that the appropriate matching of patient molecular subtypes with targeted therapeutic agents will have superior efficacy with less toxicity, thereby improving clinical outcomes. The need for robust breast cancer subgroups that further resolve the heterogeneity of existing classification schemes [18,19] motivated the development of an integrated genome-driven classification within the METABRIC cohort, as described by Curtis *et al.* [4■]. This novel classification integrates the genomic and transcriptomic profiles of breast cancer to define 10 integrative clusters characterized by distinct clinical outcomes and subtype-specific candidate drivers. Although mutational profiles were not incorporated in the discovery of the integrative subgroups, clear patterns of cluster-specific mutational landscapes are nonetheless apparent [20]. In the original description of this study, Curtis *et al.* verified the reproducibility of the subgroups in a second cohort of 1000 cases profiled on the same platforms. In a follow-up study, Ali *et al.* [21■] described the validation of the integrative subgroups in a meta-analysis of 7500 breast cancer cases. These findings have significant implications for patient stratification and tailored treatment approaches, bringing the breast cancer field closer to the realization of precision medicine.

Attempts to define robust molecular subgroups within TNBCs, which account for some 15% of breast cancers, have also been described. In particular, analysis of the gene expression profiles of 587 cases revealed six distinct subtypes, including two basal-like groups, an immunomodulatory group, mesenchymal and mesenchymal stem-like groups, and a luminal androgen receptor (AR) subtype [22,23]. There remains a critical need for advances in understanding this deadly disease, as targeted therapies have yet to be approved and cytotoxic chemotherapy remains the standard of care [24]. Several recent efforts have begun to bridge this gap. For example, expression profiling of residual disease following neoadjvuant chemotherapy revealed prognostically relevant subgroups, wherein cases with more favorable outcome exhibited elevated expression of luminal-like genes such as *AR* and *GATA3*, whereas those with poor prognosis were characterized by cancer stem cell-like programs [25■]. Related studies based on the genomic profiling of residual disease following neo-adjuvant therapy identified potentially actionable therapeutic targets in the resistant tumor cell population for 90% (67/74) of cases [26■■]. These findings may ultimately facilitate biomarker-driven adjuvant studies to target micrometastases in TNBCs that conventional chemotherapy fails to eliminate.

CHARACTERIZING BREAST TUMOR HETEROGENEITY

In addition to studies describing the comprehensive profiling of bulk tumor tissue, recent efforts have sought to characterize intratumor heterogeneity (ITH) and phenotypic diversity by assaying individual cells or small populations of cells, as well as to evaluate spatial and temporal heterogeneity in primary and metastatic lesions or during the course of therapy. For example, Almendro *et al.* [27■] applied immunofluorescence In-situ hybridization (immuno-FISH) to characterize the topographical distribution of genomic and phenotypic

features in pre and post-treatment neo-adjuvant treated breast samples. Their data indicate that ITH was subtype-specific and that lower pre-therapy genetic diversity was associated with favorable treatment response (i.e. pathological complete response). In one of the few studies of paired primary and metastatic breast cancer, Almendro *et al.* [28■] similarly examined the extent of genomic ITH and phenotypic heterogeneity during metastatic progression using immuno-FISH. They report that genetic diversity was generally highest in distant metastases relative to primary tumors and lymph node metastases, as might be expected. However, given the challenges in studying the natural history of disease, since distant breast cancer metastases are typically detected as a recurrence following systemic therapy, as was the case for this cohort, future studies in treatment-naïve samples will be necessary to resolve a number of outstanding questions concerning tumor dynamics. Single cell genomic techniques are also enabling new insights into tumor heterogeneity and clonal evolution. In particular, Wang *et al.* [29■■] recently described the use of single nuclei sequencing in an ER-positive tumor and triple negative ductal carcinoma to characterize clonal evolution. These data suggest that aneuploidy occurs early in the clonal evolution of breast cancer, and remains a stable mark, whereas somatic point mutations evolved in a protracted manner contributing to extensive genetic diversity with elevated rates of mutation found in TNBC [29■■].

Clearly, genomic and phenotypic heterogeneity pose challenges for precision medicine and have implications for the utility of predictive assays in informing treatment stratification [30]. Future efforts should aim not only to quantify ITH, but to understand its origins and impact on biomarker validation. Moreover, approaches that circumvent the issue of tissue sampling bias by assaying circulating cell-free tumor DNA (ctDNA) or circulating tumor cells (CTCs) should be further developed, as outlined below.

TISSUE AND CIRCULATING BIOMARKERS

Precision medicine requires highly sensitive and specific biomarkers that are fit for purpose for guiding individual treatment recommendations, and thus necessitates refinement beyond the established markers (ER, PR, and HER2 receptor status). Hence, much effort continues to focus on the development of prognostic and predictive tissue-based biomarkers. For example, a recent study by Silwal-Pandit *et al.* examined the spectrum of TP53 gene mutations across the integrative subgroups [4■] and PAM50 subgroups [31] within the METABRIC cohort. TP53 mutational spectra were found to be subtype-specific and of prognostic importance in several subgroups, including IntClust 1 (ER-positive, luminal B), IntClust 4 (CNA-devoid), and IntClust 5 (HER2-positive), but not in patients with luminal A and basal-like tumors [32■]. Measures of genomic complexity, such as the complex arm aberration index (CAAI), have also been proposed to contain prognostic information [33], and recent efforts have validated the ability of this index to predict survival in breast and ovarian cancer in independent cohorts [34■]. In parallel, other studies have implicated the flap endonuclease 1 (FEN1) as a genomic and protein biomarker in breast and ovarian cancer [35].

As described in the preceding sections, genomic tools have been used to identify both prognostic and predictive biomarkers in tumor tissue [5,26■■]. However, profiling of

tumor tissue has inherent limitations as a single biopsy captures a snapshot in time, is subject to selection bias resulting from ITH, and biopsies of metastatic sites can be difficult to obtain. The genomic profiling of plasma-derived ctDNA and CTCs obtained via 'liquid biopsies' provides an alternative, noninvasive approach to detect and monitor disease progression in real time, and hence may have broad utility in the management of breast cancer [36]. Cell-free fragments of DNA are shed into the bloodstream by cells undergoing apoptosis or necrosis, and hence ctDNA is thought to comprise of a pool of DNA representative of the heterogeneity present even in occult lesions, where ctDNA levels correlate with tumor staging and prognosis [37■■]. Moreover, ctDNA detection precedes clinical and radiological detection of recurrence, allowing earlier response assessment [37■■,38■■]. Recent studies have demonstrated the application of ctDNA profiling to monitor metastatic breast cancer [39■■], to track the emergence of resistant subclones in response to targeted therapy [40■■], as well as the potential of ctDNA to serve as a biomarker in diverse malignancies [37■■]. Technological advances enabling the sensitive detection of ctDNA from small amounts of plasma indicate that this approach may be useful for disease detection and monitoring of clonal dynamics across a variety of malignancies [38■■].

Although the genomic profiling of CTCs has lagged relative to that for ctDNA and is inherently more complicated, the detection and enumeration of CTCs in the peripheral blood of metastatic breast cancer patients represents an independent prognostic marker [41]. Indeed, a recent large pooled analysis confirmed the clinical validity of CTC counts in metastatic breast cancer and did not identify a significant association with any specific molecular subgroup of primary breast tumors [42■■]. To date, comparisons of ctDNA and CTC profiles in the same patient have been limited, and it will be important to determine the extent to which they provide complementary or distinct information. Future efforts should focus on the development of circulating biomarkers for the early detection of aggressive disease.

CONCLUSION

Recent studies have provided unprecedented insight into breast cancer genome diversity, revealing distinct genome-driven subtypes, novel oncogenic drivers, and candidate biomarkers. This work has provided a framework for biological validation that has critical implications for personalized treatment paradigms. In particular, the precision with which breast cancers are diagnosed and treated will benefit from their classification into molecular subtypes that are associated with effective treatments. Although numerous targeted therapeutics are under clinical development, the realization of new treatment strategies will require target and biomarker validation in adequately powered prospective studies. In parallel, the development of highly sensitive and standardized techniques to assay circulating biomarkers will be critical for the individualized, real-time monitoring of breast tumor dynamics.

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KEY POINTS

- Advanced genomic technologies have enabled the detailed characterization of the landscape of somatic alterations in breast cancer, novel insights into disease biology, and the development of a robust genome-driven classification scheme.
- Genomic profiling can facilitate the identification of both prognostic and predictive biomarkers.
- Circulating biomarkers in the blood have the potential to become minimally invasive surrogates for tumor tissue-based biomarkers that circumvent the challenges posed by ITH and inaccessible metastatic sites.
- Such ‘liquid biopsy’ approaches to assay ctDNA can enable the dynamic monitoring of residual disease, treatment response, and potentially early detection efforts.
- Ongoing efforts should aim to harness this wealth of genomic knowledge into molecularly defined targets for therapy.