Breast cancer, an ancient disease first noted by the Egyptians more than 3500 years ago [1], is the most common cancer and the second-leading cause of death from cancer in women in the United States [2]. About 12% of women in the United States will be diagnosed during their lives with breast cancer, and it is estimated that more than 40,000 patients will die from breast cancer in 2016 in the United States [2]. The probability of receiving a breast cancer diagnosis is only 1.9% in women under the age of 50 years [2]; most women receive such a diagnosis after this age, accounting for nearly 80% of all cases of breast cancer [3]. Though considerable...
progress has occurred in the treatment of breast cancer, many treatment challenges remain. One of these challenges is overcoming the clinical heterogeneity of the disease. Breast cancer was initially thought to be homogeneous; clinical observation eventually revealed otherwise, leading to the prognosis varying from patient to patient. Cooper observed that the size of breast tumors changed with the menstrual cycle [4]. Beatson further found that removal of the ovaries could reduce the tumor size of breast cancer [5]. Currently, considerable effort is being devoted to exploring and defining the mechanisms underlying the clinical heterogeneity of breast cancer. Steinthal employed clinical staging to identify this clinical heterogeneity [6]. The development of pathologic techniques has allowed physicians and patients to obtain more information about the heterogeneity of the tumors associated with breast cancer on the cellular and tissue level. For example, Greenough applied histologic classification to assess the differences in tumor differentiation and proliferation among patients [7]. Understanding of the heterogeneity of breast cancer has been deepened by the identification of different expression levels of the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2), each of which is a key biomarker used for clinical decision making.

During the past two decades, the rapid development of genetic analysis technologies has enabled depiction of the heterogeneity of breast cancer on a genetic level [8]. Several genetic alterations have been identified, including germline BRCA mutations, which frequently occur in hereditary breast cancer [9]. Based on comprehensive gene-expression profiling, breast cancer has been classified into five main categories: luminal A, luminal B, Her2-enriched (also called Her2-related), claudin-low, and basal-like [10].

From clinical observation to testing for genetic mutations, a lengthy and steep learning curve has been experienced in understanding the tumor heterogeneity of breast cancer (Fig. 1). Various studies have demonstrated that heterogeneity can occur either among different patients with the same tumor type (intertumor heterogeneity) or within the same patient (intratumor heterogeneity) [11–13]. Traditionally, intertumor heterogeneity was thought to be the largest barrier in the treatment of breast cancer. Effective and individualized therapeutic plans have been established based on the understanding of intertumor heterogeneity. For example, adjuvant endocrine therapy is widely prescribed for patients who have hormone receptor-positive tumors. However, apart from intertumor heterogeneity, it should be noted that intratumor heterogeneity also poses a tremendous challenge for treatment selection. In fact, ER, PR, and Her-2 are expressed differently in different regions within the same tumor as well as between the matched primary tumors and metastatic lesions [14]. To further add to this complexity, microenvironmental components of tumors (such as stromal cells and extracellular matrix) are highly variable among different patients [15] and impact the effectiveness of treatment. In the clinical setting, patients’ tumors may have the same molecular classification and receive the same treatment, yet patients may experience very different outcomes. Some patients acquire resistance to therapies such as endocrine therapy and targeted therapy during treatment in spite of the initial efficacy of these approaches [16, 17]. Therefore, it is important to identify potential intertumor heterogeneity and intratumor heterogeneity to devise new treatment plans with new therapeutic targets.

![Figure 1](image-url)
In previous studies, cumulative exposure to carcinogenic factors led to elevations in chromosomal instability and cancer-specific driver mutations [18, 19], both of which lead to abnormal gene expression [12, 20, 21]. The genetic alterations might be different across cancer cell subgroups. Each of these alterations (alone or in different combinations) endows different cancer cell subgroups with different features [22, 23]; cancer cell subgroups form solid tumors with distinct clinical (i.e., morphologic and prognostic) features. Therefore, using the origins of heterogeneity as a starting point, both intertumor and intratumor heterogeneity can be detected. Powerful technologies such as genomic analysis technology, molecular and pathologic technology, and imaging techniques have been used to detect breast cancer heterogeneity and inspect its dynamic changes (Fig. 2). This review summarizes recent advances in detecting and monitoring heterogeneity in breast cancer and is split into three sections, each of which reviews one of these technologies. At the end of this review, we will discuss how these new techniques have improved our understanding of the heterogeneity of breast cancer and its clinical management.

**Genomic Analysis**

Genomic analysis is an important tool for analyzing the heterogeneity of tumors. As early as 1978, karyotyping was used for the detection of genomic abnormalities [24]. However, because DNA samples derived from a breast tumor are a mixture of different DNA from heterogeneous tumor cells, it was difficult to identify the degree of genomic heterogeneity of cancer cells. Considerable progress has occurred with respect to DNA sequencing and the development of detection methods for genomic abnormalities. Recent technological advances have included the microarray, next-generation sequencing (NGS), and in situ sequencing. Each of these captures the genomic diversity of breast cancer cells.

**In situ Hybridization**

In situ hybridization (ISH), a common technique widely used to detect gene number copy alterations, localizes a specific DNA or RNA sequence in tissue by using labeled probes with known sequences [25]. ISH plays an important
Role in detecting both intertumor and intratumor gene heterogeneity in breast cancer. For example, the fluorescence in situ hybridization (FISH) assay is considered the “gold standard” in evaluating HER2 gene status in patients with breast cancer [26]. The FISH assay has also been widely used to identify gene copy number and distribution heterogeneity. For example, Janiszewska and colleagues employed FISH to assess the spatial heterogeneity of cellular genetic diversity and the changes in the frequency and topology of the PIK3CA mutation and Her-2 amplification within Her-2-positive breast cancer during neo-adjuvant therapy [27]. Furthermore, the development of the multicolor FISH (mFISH) assay makes it possible to simultaneously detect the degree of intertumor and intratumor heterogeneity in several genes [28, 29]. Li and colleagues used mFISH to detect copy number aberrations in four genes related to cell cycles in patients with breast cancer [29]. More recently, ISH was employed to identify heterogeneous expression in RNA molecules in breast cancer, providing information about tissue-specific and cell-specific expression [30].

Gene-Expression Profiling

Gene-expression profiling is an important method of detecting gene-expression heterogeneity in patients with breast cancer. Genetic microarrays and 21-gene expression assays are the most frequently used techniques in clinical detection of RNA-expression heterogeneity among patients. A gene microarray is a collection of microscopic probes attached to a solid surface. The concept was first introduced by Schena in 1995 [31], and is based on the ability of DNA to find and spontaneously bind its complementary sequence in a reversible way with high specificity [32]. The technique can simultaneously measure the expression levels of thousands of genes and identify differentially expressed genes among different patients with cancer [33, 34]. Gene microarrays have been used to identify a number of differentially expressed genes [33]. As early as 2000, Perou and colleagues performed pattern analysis for gene expression in breast cancer using complementary DNA microarrays, initially discovering five major intrinsic gene signatures: luminal A, luminal B, Her-2-enriched, claudin-low, and basal-like [10]. Gene microarrays could further be used to predict response to chemotherapy and risk of recurrence by inspecting the expression level of genes related to therapy resistance and recurrence [34, 35]. Recently, microarrays have been frequently used to screen noncoding RNAs related to breast cancer and identify new tumor subtype markers [36–38]. Though the microarray can attain the level of high-throughput analysis of gene expression, it cannot provide in situ information about gene expression.

The 21-gene expression assay is based on reverse transcriptase polymerase chain reaction (RT-PCR), which is able to qualitatively detect gene expression. In 2004, Paik and colleagues first developed a scoring system based on 21 prospectively selected genes in paraffin-embedded tumor tissue to quantify the likelihood of distant recurrence in patients with node-negative, ER-positive breast cancer [39]. They further demonstrated that the 21-gene recurrence score could also be a powerful tool to predict the magnitude of benefit from chemotherapy [40]. Several additional studies have shown that the use of the 21-gene expression assay is cost-effective in patients whose cancer has not metastasized to the lymph nodes [41–43]. The 21-gene expression assay has been widely used to predict tumor heterogeneity in disease recurrence and response to chemotherapy [44–47]. Various studies have demonstrated that 21-gene recurrence score changed the clinical–pathological adjuvant chemotherapy recommendation [48–53].

Gene Sequencing

In 1977, Frederick Sanger first introduced his DNA sequencing technique [54]. After 30 years of development, novel sequencing technologies with reduced costs and increasing throughput have been developed. NGS is a newly developed high-throughput technology that has revolutionized cancer genome sequencing by providing detailed characterization of the cancer genome and epigenomic information about breast cancer [55–57]. NGS makes it possible to perform large-scale analysis of cancer genes, leading to the discovery of new genes associated with breast cancer and of the heterogeneity of individual tumors [58]. Stephens and colleagues identified several new cancer genes in breast cancer with the help of NGS [18]. Furthermore, based on the NGS results, additional bioinformatic tools will allow mining of the sequencing data and unveiling of the evolution process for cancer cell subgroups within breast cancer [59]. The phylogenetic tree for breast cancer evolution provides an intuition into the dynamic evolutionary course of intratumor heterogeneity [22, 23, 60]. In combination with flow-based cell sorting and efficient whole-genome amplification (WGA), NGS can be used to detect the genomic alteration of single tumor cells [22]. NGS-based liquid biopsy is currently an area of great research interest and will ideally facilitate the early diagnosis of intratumor heterogeneity and continuing surveillance of dynamic changes [61–63]. Murtaza and colleagues successfully inspected the dynamic changes in genomic architecture derived from circulating tumor cells during adjuvant chemotherapy and identified genes related to resistance to chemotherapy [64]. Although NGS can roughly identify spatial heterogeneity in genomic alterations through
multiregional sequencing, it cannot provide information about in situ gene expression [65, 66].

Recently, Lee et al. developed a new technique, fluorescent in situ sequencing of RNA, for gene expression profiling [67, 68] through conversion of RNA into cross-linked cDNA amplicons and manual sequencing on a confocal microscope. This technique is still in its experimental phase, but has broad prospects for helping researchers further understand intratumor heterogeneity.

**Pathologic Analysis**

Pathologic analysis plays important roles in the diagnosis and subtyping of breast cancer. Developments in pathologic technologies have promoted greater understanding of both intertumor and intratumor heterogeneity. Pathologic analysis can now combine morphology with molecular biology, providing new insights into breast cancer heterogeneity.

Pathologic analysis techniques such as immunohistochemistry (IHC) and immunofluorescence (IF) have been widely used for assessing therapeutic biomarkers of breast cancer and identifying subsets of patients with different outcomes [69, 70]. IHC markers such as ER, PR, Her-2, and proliferation markers could divide breast cancer cases into groups remarkably similar to subtypes defined by gene expression studies [71–73]; however, these are qualitative analyses. Quantifying tumor heterogeneity has become more urgent with these developments in pathology’s capabilities. Some studies have attempted to conduct semiquantitative analysis using conventional IHC and successfully identified different degrees of intratumor heterogeneity [74, 75]. Potts and colleagues combined semiquantitative analysis with ecology diversity statistics to evaluate the heterogeneity on IHC-stained breast cancer samples and identified new features in HER2 expression among different patients [74].

Though conventional pathologic analysis methods have great value in evaluating the heterogeneity of breast cancer, due to its limitations in quantitative analysis and multilabeled staining, these methods are not able to completely reveal the heterogeneity of breast cancer, especially intratumor heterogeneity.

Recently, nanotechnology has been regarded as a promising tool to illustrate the heterogeneity of breast cancer. Optical-based nanoparticle imaging, such as quantum dots-based immunohistochemistry (QDs-IHC), is an important branch of nanotechnology as applied in medicine. Most of the QDs are semiconductor nanocrystals that have properties including high fluorescence intensity, strong resistance to photobleaching and chemical degradation, size-tunable emission wavelengths, and simultaneous multiple fluorescence under a single excitation source [76, 77]. Due to these properties, QDs-IHC is a powerful tool to detect breast cancer heterogeneity, as it can provide in situ information for multiple biomarkers (Fig. 3) [78]. Chen and colleagues successfully visualized Her-2 and ER simultaneously with QD-based imaging; this technique very clearly displayed the heterogeneous expression of these markers in breast cancer [79]. Furthermore, Peng and colleagues obtained multidimensional information both from cancer cells and from the tumor microenvironment through QDs-IHC [80]. When performing multiplex imaging of various key immunomarkers such as epidermal growth factor receptor (EGFR), Her-2, and the Ki-67 protein simultaneously, we found new tumor characteristics that were associated with breast cancer prognosis [81–83]. To summarize, QDs-IHC provides new insight into the heterogeneity of breast cancer and will play an important role in individualized breast cancer treatment.

**Imaging Analysis**

A variety of imaging techniques exist for the screening and diagnosis of breast cancer. Mammography, ultrasound, magnetic resonance imaging (MRI), and positron emission tomography (PET) are the most common techniques for breast cancer imaging. These imaging techniques can reveal the diverse characteristics of breast cancer (Fig. 4). With the development of technology and deeper recognition of breast cancer, some imaging techniques are further used to detect breast cancer heterogeneity. This section summarizes recent advances in this area.

**X-ray-Based Imaging**

X-ray-based imaging includes techniques such as mammography, computed tomography, and new imaging techniques such as digital breast tomosynthesis (DBT). Mammography has been widely used in breast cancer screening and allows physicians to obtain information about calcifications and breast cancer’s morphologic features. The mass shape (round, oval, lobular irregular, and obscured) on mammography has been associated with the Oncotype Dx (a breast cancer array incorporating the mRNA expression of 21 genes) recurrence score [84]. However, very little research to date has evaluated the application of mammography in detecting inter- or intratumor heterogeneity due to the limited information yielded by the imaging technique.

DBT, first introduced in 2011, improved on standard mammography by increasing breast cancer detection rates [85]. However, limited evidence exists of its use in
detecting heterogeneity in breast cancer. Computed tomography (CT) allows scanning of the entire breast in thin slices [86, 87]. The use of contrast material with CT allows more information to be obtained about the characteristics of breast cancer in a particular patient. Tamaki and colleagues found that CT findings could serve as predictive prognostic factors when correlated with histological characteristics [88]. However, due to its radioactivity and low...
sensitivity, CT is not as commonly used as MRI for detection and staging of breast cancer or for potential determination of heterogeneity.

**Ultrasound**

With the development of ultrasound technology, two relatively new techniques, contrast-enhanced ultrasound (CEUS) and elastography, have added complementary information to breast cancer diagnosis. Aside from morphological features, CEUS can provide more information about tumor angiogenesis.

Elastography is based on the depiction of tissue stiffness, which in breast cancer has been associated with interactions among tumor cells, stromal cells, and the extracellular matrix [89]. These properties are associated with heterogeneity in breast cancer, and many authors have tried to use ultrasound to detect breast cancer heterogeneity. Elastography also demonstrated that some sonographic features are associated with pathologic features, including histologic grade [90]; however, elastography was not useful for the correlation of mechanical elasticity with breast cancer subtype [90–92].

CEUS was reported to be a useful tool for correlating imaging features with pathological characteristics. Several studies identified heterogeneity in the expression of vascular endothelial growth factor (VEGF) using CEUS [93, 94]. Masumoto and colleagues found that perfusion parameters on CEUS were significantly associated with ER, Her-2, and Ki-67 status [95]. This result is consistent with other studies [96, 97]. CEUS also achieved high accuracy in predicting the heterogeneity of the response of breast cancer to neoadjuvant chemotherapy [98, 99]. The use of microbubbles labeled by specific antibodies also allows CEUS to achieve the level of detail of molecular imaging. Sorace and colleagues successfully depicted microvessel density within tumors using multitargeted microbubbles conjugated with antibodies against mouse Avβ3 integrin, P-selectin, and vascular endothelial growth factor receptor 2 (VEGFR2) [100]. Based on these results, ultrasound will be a powerful tool for detecting both intertumor and intratumor heterogeneity of breast cancer.

**Magnetic Resonance Imaging**

Due to its excellent soft-tissue contrast and high sensitivity, MRI has been widely used in diagnosis of breast cancer as a complementary imaging technique to mammography and ultrasound [101]. Parameters such as tumor size, morphology, and shape can be obtained from MR images. Dynamic contrast-enhanced MRI (DCE-MRI) even allows the investigation of microvascular structure and kinetic characterization (e.g., maximum relative enhancement, time to peak, area under the curve) as well as statistical measurement of texture enhancement (e.g., gray level co-occurrence matrix) [102]. These parameters reflect intratumor characteristics including growth patterns, angiogenesis, and permeability. Therefore, MRI is a feasible tool for evaluating breast cancer heterogeneity.

Numerous studies have been conducted to explore the application of MRI in screening for breast cancer heterogeneity. Yun and colleagues demonstrated that MRI parameters such as standard deviation and kurtosis of apparent diffusion coefficient (ADC) values were closely related to intratumor spatial heterogeneity of necrosis patterns and vascularity in MCF-7 and MDA-MB-231 xenograft models [103]. Different breast cancer subtypes exhibit different growth patterns and angiogenesis [104, 105]. Therefore, it is possible to correlate MRI parameters with molecular subtypes of breast cancer. In a retrospective analysis of 102 patients, Chang and colleagues used receiver operating characteristic (ROC) curve analysis in conjunction with MRI to identify region-based features of tumors and achieve high accuracy in breast cancer classification [106]. ADC was also reported to be associated with breast cancer subtypes [107–110]. Some studies further attempted to correlate imaging features with expression information. Sutton and colleagues found that MR-derived image features (such as kurtosis) were significantly related to the Oncotype Dx recurrence score [111]. Other studies have reached similar conclusions [84]. MRI is also a powerful tool to predict the heterogeneity of the response to anticancer therapy among patients [112, 113]. Ashraf and colleagues determined that DCE-MRI kinetic statistics could predict response to neoadjuvant chemotherapy [112]. Another study explored the use of chemical exchange saturation transfer MRI (CEST-MRI) to characterize the metabolic heterogeneity within tumors [114]. CEST contrast was linearly correlated with nicotinamide adenine dinucleotide hydrate (NADH) concentration and the NADH redox ratio [100]. These results might confirm the usefulness of a novel noninvasive imaging surrogate to screen for metabolic heterogeneity in breast cancer.

**Molecular Imaging**

Molecular imaging is an emerging discipline with great promise in detecting intertumor and intratumor expression patterns of key molecules in breast cancer. Molecular imaging depends greatly on labeled biomarkers; these can be molecules, proteins, or antibodies. By tracing these labeled biomarkers, we can evaluate heterogeneity in biochemical changes, cellular physiology, cellular function, and metabolism within breast cancer [115].

PET is the most frequently used molecular imaging technique. PET can be used to assess various properties
of tumors with an appropriate radiotracer, such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) for metabolism, $^{18}$F-fluorothymidine ($^{18}$F-FLT) for proliferation, and $^{18}$F-fluoroestradiol ($^{18}$F-FES) for ER status [115, 116]. Therefore, it can be a powerful tool to identify and inspect the dynamic changes in intratumor heterogeneity of breast cancer.

Several studies found that different $^{18}$F-FDG PET features could be translated into the immunohistochemical characteristics of breast cancer [117–119]. For example, in a retrospective analysis of 171 patients, Groheux and colleagues demonstrated that SUVmax, SUVmean, and TLG were significantly associated with the three phenotype subgroups (triple-negative, Her-2-positive, and ER-positive/Her-2-negative breast cancer) [118]. Koo et al. found that $^{18}$F-FDG uptake was correlated with a high Ki-67 index in triple-negative breast cancer [117]. PET based on $^{18}$F-FES or $^{89}$Zr-trastuzumab could even achieve dynamic monitoring of ER and Her-2 status during concomitant endocrine and trastuzumab therapy. In a study by van Kruchten and colleagues, $^{18}$F-FES PET was used to determine the dose needed for ER antagonists to completely abolish ER [120]. Currin and coworkers demonstrated restoration of endocrine sensitivity after initial endocrine resistance with the help of $^{18}$F-FES PET [121]. In another study, Her-2-based PET was used to help explore heterogeneity during Her-2 mapping of metastatic disease and to help select patients who may demonstrate a response to trastuzumab therapy [122]. Several studies further demonstrated that PET successfully identified spatial metabolic heterogeneity in breast cancer [123]. With the help of $^{18}$F-FLT, intratumor proliferation heterogeneity was imaged using PET for assessing the response to neoadjuvant chemotherapy [124, 125].

Besides PET, QDs-based imaging is also a promising molecular imaging technique (discussed earlier in the Pathologic Analysis section). QDs conjugated with various biomarkers could image different targets in breast cancer [77, 78], and they have shown great potential in molecular imaging. Tada and colleagues successfully applied anti-Her-2 antibody-conjugated QDs to obtain images of Her-2 overexpression in breast cancer xenografts [126]. However, in vivo fluorescence imaging is affected by tissue depth. Some authors have tried to link QDs-based imaging with other imaging techniques to solve this problem. For example, Ma and colleagues successfully achieved in vivo multimodality imaging using a multilayered, core/shell nanoprobe based on magnetic nanoparticles (MNP)s and QDs [127].

QDs-based imaging is relatively immature for clinical application. However, QDs-based imaging will have a future role in molecular imaging for breast cancer due to its optimal applicability in imaging acquisition and ability to quantify multiple biomarkers.

**Progress in Understanding of Heterogeneity**

The technological advances reported in this paper have greatly increased our understanding of intertumor heterogeneity. Based on analysis of the copy number and gene-expression profiling data from approximately 2000 breast cancer patients, Curtis et al. identified 10 novel molecular subgroups with distinct clinical outcomes [128]. The 21-gene assay based on gene-expression profiling could provide additional prognostic information and predict benefit from adjuvant chemotherapy in ER-positive patients [47]. Another example is QDs-IHC, with which we revealed intertumor heterogeneity pattern by quantitatively analyzing traditional biomarkers such as EGFR, Her-2, and Ki-67 [81, 82]. Furthermore, greater in-depth knowledge of intratumor heterogeneity has resulted from these various new technologies. NGS offers the compelling advantage of providing an assessment of intratumor heterogeneity. A number of NGS studies demonstrated that breast tumors are composed of several subclones harboring different somatic mutations, copy number aberrations, and chromosomal rearrangements [19, 66]. Further NGS analysis found that clonal competition and selective pressure from the microenvironment and therapy led to a state of dynamic change for these subclones [18, 22, 129]. Using integrated NGS and digital RNA profiling, Balko and colleagues discovered that the genomic landscape of residual cancer after neoadjuvant chemotherapy was different from that of the pretreatment specimens, with increased enrichment in MCL1 amplification, PTEN deletions and/or mutations, JAK2 amplifications, and CDK6/CCND1–3 amplification [130]. With the help of FISH, Janiszewska and colleagues found a dramatic increase in the relative frequency of PIK3CA-mutant cells after neoadjuvant chemotherapy [27]. Furthermore, NGS analyses of primary breast tumors and matched metastatic lesions have a distinct genomic landscape [131]. Based on these findings, we can identify new therapeutic targets and develop a more detailed, targeted treatment plan. In actuality, $^{18}$F-FES PET has been used to monitor endocrine resistance during endocrine therapy to help create more efficient treatment plans [121]. However, overcoming intratumor heterogeneity will take considerably more research.

The microenvironment in which cancer cells exist is another important component of breast cancer and plays an essential role in cancer progression [15], and it can pose selective pressure on cancer cells by regulating cancer cell–signal transduction and gene expression. Developments in these techniques (mentioned above) also deepened our understanding of heterogeneity in a microenvironment. Conventional pathologic analysis and IHC have identified various stromal biomarkers such as COX-2, MMP-1, and...
Syndecan-1 that are associated with breast cancer prognosis [132]. Furthermore, with the help of QDs-IHC, simultaneous imaging was possible of EGFR and collagen IV in triple-negative breast cancer. EGFR and collagen IV could act as predictors of clinical outcomes [82]. Genomic analysis was also a powerful tool. A 163-gene prognosticator generated from stromal gene expression profiling was highly prognostic in Her-2-positive cases of breast cancer [133].

Future Perspectives

Precision medicine has received greater attention in recent years, especially in the field of cancer treatment [134]. As part of this new approach, effective detection of heterogeneity in breast cancer, both inter- and intratumor, has become imperative. In terms of genomic analysis, new analysis techniques and genomic data mining that will enable us to identify new targets for therapy are the primary future directions of breast cancer treatment. With regard to pathologic analysis, quantitative analysis of the heterogeneity of tumor(s) in breast cancer will be an important element in finding factors that are associated with prognosis and sensitivity (or resistance) to therapy. Molecular imaging shows great promise in the detection of heterogeneity in breast cancer; this imaging technique could combine morphological and molecular heterogeneity with functional heterogeneity, enabling more in-depth understanding of intratumor heterogeneity. Collectively, development of these techniques has the potential to promote considerable progress in precision medicine with respect to detection of heterogeneity in breast cancer, and potential improvements in treatment.

Conflict of Interest

None declared.

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