

# Met induces diverse mammary carcinomas in mice and is associated with human basal breast cancer

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**Understanding the signaling pathways that drive aggressive breast cancers is critical to the development of effective therapeutics. The oncogene MET is associated with decreased survival in breast cancer, yet the role that MET plays in the various breast cancer subtypes is unclear. We describe a knockin mouse with mutationally activated Met (Met<sup>mut</sup>) that develops a high incidence of diverse mammary tumors with basal characteristics, including metaplasia, absence of progesterone receptor and ERBB2 expression, and expression of cytokeratin 5. With gene expression and tissue microarray analysis, we show that high MET expression in human breast cancers significantly correlated with estrogen receptor negative/ERBB2 negative tumors and with basal breast cancers. Few treatment options exist for breast cancers of the basal or trastuzumab-resistant ERBB2 subtypes. We conclude from these studies that MET may play a critical role in the development of the most aggressive breast cancers and may be a rational therapeutic target.**

ErbB2 | mouse model

**B**reast cancer affects >200,000 women in the United States each year, yet the mortality rate is rapidly declining with earlier detection and the availability of targeted therapies. However, tumors that do not express estrogen receptor (ER), progesterone receptor (PR), or both are less differentiated, more clinically aggressive, and less likely to respond to hormone-targeted therapy (1, 2). Moreover, 20–30% of all breast cancers overexpress human epidermal growth factor receptor-2 (HER2/ERBB2) and are associated with reduced survival (3). Those tumors that no longer depend on ER/PR and ERBB2 signaling have the poorest prognosis and no targeted therapeutic options (4). Recently, gene expression studies have identified several distinct breast cancer subtypes that correlate with clinical outcome (5, 6). These molecular subtypes include three main groups of ER negative tumors, including basal, ERBB2, and the normal-like/unclassified subtype, and at least two types of ER positive tumors (luminal A and luminal B). Patients with tumors classified as basal or ERBB2 have significantly shorter survival rates compared with those with the ER<sup>+</sup> luminal A subtype. Metaplastic breast carcinomas have various combinations of adenocarcinoma, mesenchymal, and epithelial features and are associated with the basal subtype (7, 8). These classifications have improved our understanding of the unique molecular signatures present in breast cancer and how they may relate to patient prognosis.

The receptor tyrosine kinase Met is a well-known oncogene that is involved in the progression and metastasis of most solid human cancers ([www.vai.org/metandcancer](http://www.vai.org/metandcancer)) (9). Under normal physiological conditions, Met is expressed by epithelial cells and activated through paracrine ligand binding of hepatocyte growth factor/scatter factor (HGF/SF). In neoplastic conditions, aberrant Met activity occurs through numerous mechanisms, including overexpression of Met, HGF/SF, or both, autocrine signaling,

or mutational activation. In breast cancer, MET is overexpressed in 20–30% of cases, is a strong, independent predictor of decreased survival (10–12), and correlates with poor patient outcome, independent of HER2/ERBB2 expression (13). Met signaling may therefore have a unique function in breast cancer progression distinct from ERBB2 signaling.

We investigated the role of Met in mammary tumorigenesis, through a mouse model of mutationally activated Met. This model contains activating missense mutations within the tyrosine kinase domain (M1248T/L1193V) that have been knocked into the endogenous Met locus and are referred to as Met<sup>mut</sup> (14). Here, we report that activated Met (on a FVB/N background) induced a high incidence of mammary tumors with diverse histopathological phenotypes. High levels of *Met* amplification were present as extrachromosomal double minutes in the tumors. Most notable was that several mice developed multiple mammary tumors with distinct histopathologies and ER/PR/ErbB2 signatures. Met<sup>mut</sup> tumors were ER<sup>+</sup>/PR<sup>-</sup>, half did not express ErbB2, and several expressed the basal marker cytokeratin 5 (CK5). These results led us to examine MET expression in human breast cancer subtypes. Our analyses of human breast cancer expression data and tissue microarrays revealed that high MET expression correlates with ER<sup>-</sup>/ERBB2<sup>-</sup> tumors and the basal subtype.

Here, we show that a single oncogene, such as Met, is able to induce a spectrum of mammary cancers (solid adenocarcinomas, adenosquamous carcinomas, and myoepitheliomas) with histological, cytogenetic, and ER/ErbB2 characteristics that are present in aggressive human breast cancers. This is a valuable model for aggressive human breast cancers that express high levels of MET. Moreover, our mouse model, in conjunction with the human breast cancer analysis, indicates that MET may be a significant therapeutic target for one of the most aggressive breast cancer subtypes.

## Results

**Mutationally Activated Met Induces Diverse Mammary Adenocarcinomas.** We wished to investigate the role of the Met oncogene in mammary tumorigenesis. Earlier our lab created a transgenic model of mutationally activated Met that developed metastatic mammary tumors in the founder mice, yet they failed to transmit (15). We previously described a knockin mouse model of mutationally activated Met generated on a C57BL/6;129/SV back-

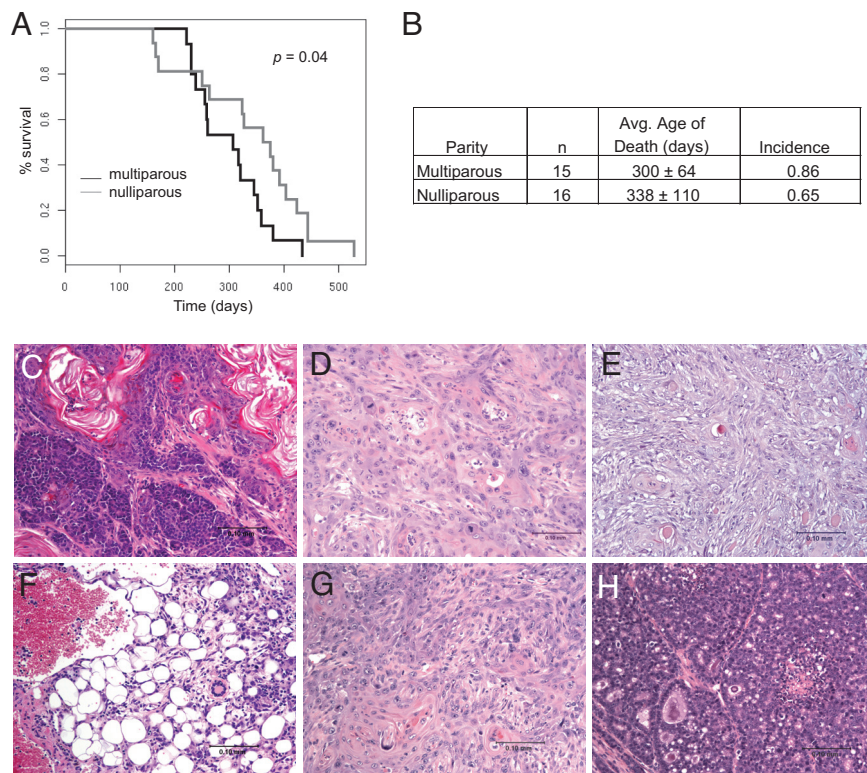
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**Fig. 1.** Mutationally activated *Met* induces diverse mammary tumors. (A) Kaplan–Meier analysis demonstrated a slight difference in age of death between multiparous and nulliparous females ( $P = 0.04$ ). (B) A high incidence of mammary tumor development was observed in both multiparous and nulliparous females. (C) Mammary adenosquamous carcinoma with solid and tubular patterns (animal 28). (D) Mammary squamous cell carcinoma (animal 6) that had significant karyomegaly. (E) Mammary myoepithelioma (animal 2). (F) Hemangioma with squamous metaplasia and (H) an adenocarcinoma with solid patterns both observed in different mammary glands of animal 13 (solid patterns not shown in image).

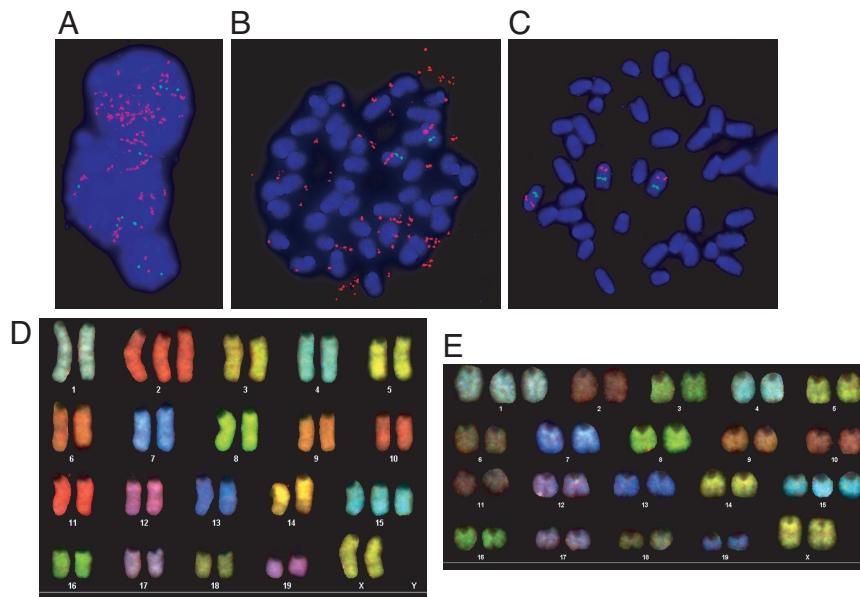
ground that developed sarcomas, lymphomas, and carcinomas, but failed to generate mammary tumors (14). Because parous FVB/N females commonly develop hyperplasia (16), we bred the M1248T/L1193V mutant line congenically onto the FVB/N background. This model is referred to as *Met*<sup>mut</sup> and contains activating missense mutations within the tyrosine kinase domain (M1248T/L1193V). These mutations are knocked into the genomic *Met* locus and, therefore, expressed under the endogenous *Met* promoter. When maintained as heterozygotes, these mice develop aggressive mammary tumors. Both nulliparous ( $n = 16$ ) and multiparous females ( $n = 15$ ) developed mammary tumors with high penetrance, and Kaplan–Meier analysis revealed only a slight difference in the average age of tumor onset (Fig. 1 *A* and *B*).

Analysis of mammary pads from 6- and 8-month-old females showed no evidence of preneoplastic growth, indicating that tumor growth is extremely rapid after initiation. A surprising variety of histopathological phenotypes were identified (Fig. 1 *C–H* and Table S1). Solid features were present in 30% of the tumors, but in several cases the solid phenotype was intermixed with squamous metaplastic cells (Fig. 1*C*). Significant squamous metaplasia was observed in 65% of mammary tumors (Fig. 1*D*), and three myoepitheliomas were identified (Fig. 1*E*). In addition to mammary neoplasia, five mice developed undifferentiated sarcomas (Fig. 1*F*), as was observed on the B6 background (14). Interestingly, four mice developed two tumors with quite different histopathological phenotypes. For example, one animal developed both an adenocarcinoma with squamous metaplasia and an adenocarcinoma with solid patterns (Fig. 1 *G* and *H*). This may be explained if *Met* mediates transformation in early stages of mammary development and variation in the cell lineages allows for the development of distinct tumor types.

#### ***Met* Amplification Is a Primary Chromosomal Alteration in *Met*<sup>mut</sup> Mammary Adenocarcinomas.**

In both human papillary renal tumors and mice with germline-activating mutations, nonrandom duplication of the mutant *Met* allele was observed (14, 17). To determine if similar chromosomal events were present in the *Met*<sup>mut</sup> mammary tumors, we performed interphase dual-color FISH on six mammary tumors with various histologies. Using a BAC clone specific for the *Met* locus on chromosome (Chr) 6 and a control probe on Chr 6 allowed us to distinguish between a gain of Chr 6 and localized amplification of the *Met* locus. In six tumors examined, we observed up to 50 copies of *Met* (Fig. 2*A* and Table S2). The high levels of *Met* amplification were observed in cells with extremely large nuclei that composed 2–5% of the tumor. Trisomy and larger gains of Chr 6 also were detected. We performed metaphase FISH analysis on three primary tumors (Table S3) to assess if the amplification was extrachromosomal. In all cases, the majority of *Met* amplifications were present as extrachromosomal double minutes (Fig. 2*B*). Only one tumor showed intrachromosomal and extrachromosomal *Met* amplification by metaphase FISH (Table S3). However, we did identify several metaphases containing trisomy 6 and no double minutes (Fig. 2*C*). Curiously, we did observe a higher copy number of Chr 6 in interphase FISH compared with that observed in metaphase FISH, but some tetraploid metaphases did not spread sufficiently and were unanalyzable for metaphase FISH. Therefore, the amplification of *Met* and gain of Chr 6 may be higher than that detected by metaphase FISH.

We examined the chromosomal region around the *Met* locus and observed that the *Wnt2* proto-oncogene is 0.5 Mb from *Met*. Interphase FISH analysis revealed that the double minutes also contained *Wnt2*. However, further analysis determined that



**Fig. 2.** *Met* amplification is a primary chromosomal alteration present in *Met*<sup>mut</sup> mammary tumors. (A) Relative copy number of *Met* was measured using FISH. Photomicrographs with *Met* probe (red), control probe (green), and DAPI (blue) are shown for animal 17. One nuclei (bottom) is diploid, whereas the other two nuclei have  $\approx 18$  (middle) and  $>50$  (top) copies of *Met*. (B) Metaphase FISH of a mammary adenocarcinoma (animal 29) with two copies of Chr 6 and  $\approx 49$  copies of *Met* in double minute chromosomes. (C) Metaphase FISH of a mammary adenocarcinoma (animal 30) with trisomy of Chr 6. (D) Spectral karyotyping of a myoepithelioma from animal 29 with trisomy of Chr 2 and 15. (E) Spectral karyotyping of a mammary adenocarcinoma from animal 25 with trisomy of Chr 1 and 15.

*Wnt2* expression was not increased in these tumors, yet *Met* expression was increased.

To determine what other chromosomal changes occur in *Met*<sup>mut</sup> tumors, we performed spectral karyotyping on three adenocarcinomas. We observed trisomy of Chr 1, 2, and 15 frequently (Fig. 2 *D* and *E* and Table S3) and a low occurrence of trisomy of Chr 3, 6, and 13. The lack of numerous chromosomal aberrations suggests that *Met* amplification is sufficient to avoid the need for extensive instability ordinarily associated with mammary tumorigenesis. These results and a study showing high levels of *Met* amplification in *Brcal/Trp-53* mammary tumors (18) indicate that *Met* amplification may be a common event in murine mammary tumorigenesis. However, interphase FISH was performed on a human breast cancer tissue microarray, and *Met* amplification was not observed.

#### **Met Is Highly Expressed in Tumor Cells that Are PR and ErbB2 Negative.**

To determine the ER/PR/ErbB2 profile of *Met*-induced tumors, we performed immunohistochemical staining on 12 tumors with various histologies and normal tissue sections. All of the tumors expressed high levels of *Met* (Fig. 3), which was confirmed through Western blot analysis (Fig. S1). The majority of tumors (11 of 12) were ER<sup>+</sup> (Fig. 3 and Table S4). This result was unexpected given that genetically engineered mouse models commonly develop ER<sup>-</sup> mammary tumors (19). In addition, we observed that all *Met*<sup>mut</sup> tumors lacked PR expression. The absence of PR may reflect a lack of ER activity or the up-regulation of growth factor signaling pathways (20). When we examined ErbB2 expression, we found that half of the tumors were ErbB2 negative. We also observed that a single animal could develop tumors with unique ER/PR/ErbB2 profiles. For instance, animal 26 developed two carcinomas, one which was ER<sup>+</sup>/PR<sup>-</sup>/ErbB2<sup>-</sup> (Fig. 3A) and one which was ER<sup>+</sup>/PR<sup>-</sup>/ErbB2<sup>+</sup> (Fig. 3B). Remarkably, a single oncogene, such as *Met*, is able to induce diverse tumors with unique histologic features and signaling requirements within a single animal.

Within the *Met*<sup>mut</sup> mammary tumors, we often observed ductal structures that appeared more differentiated. When we

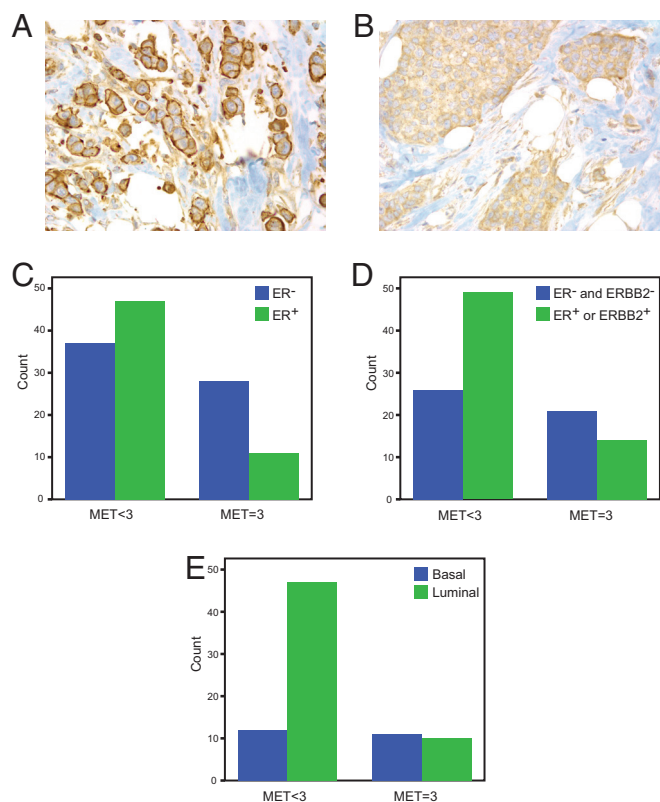
carefully evaluated these structures compared with adjacent anaplastic regions, we observed an inverse relationship between *Met* and ER/PR/ErbB2 expression within individual cells. As seen in Fig. 3C, high ER, PR, and ErbB2 expression was observed in a hyperplastic ductal structure, yet *Met* expression was negligible. Conversely, high levels of *Met* expression were observed in the surrounding tumor regions, whereas PR and ErbB2 expression was diminished and ER expression decreased. This inverse relationship with *Met* and ER/PR/ErbB2 expression occurred only in hyperplastic regions within the tumors. Expression of *Met*, in addition to ER, PR, and ErbB2, was observed in hyperplastic ducts outside the tumor borders (Fig. S2). We hypothesize that increased *Met* signaling compensates for the decrease or absence of ER, PR, or ErbB2 signaling within tumorigenic cells.

#### **MET Expression Is Enhanced in Basal and ErbB2 Breast Cancer Subtypes.**

Basal-like breast carcinomas are heterogeneous and have distinct histological features, such as myoepithelial and metaplastic differentiation. In addition, basal-like tumors typically express genes characteristic of basal epithelial cells (i.e., cytokeratins 5, 14, 15, and 17) (21). Because *Met*<sup>mut</sup> tumors consist of myoepithelial and metaplastic features and are often PR<sup>-</sup>/ErbB2<sup>-</sup>, we examined *Met*<sup>mut</sup> tumors for expression of the basal marker CK5. We detected CK5 expression in the majority of the *Met*<sup>mut</sup> tumors but not in solid regions within the tumors (Fig. S3). The above results suggested that the *Met*<sup>mut</sup> tumors may have basal-like characteristics and led us to examine *MET* gene expression in human basal and nonbasal cancers.

Examination of *MET* expression in an existing human breast cancer expression dataset (22) indicated that *MET* was significantly expressed in basal-like cancers compared with nonbasal cancers ( $P = 0.007$ , Fig. 4A). In addition, there were two subsets in the basal-like category: one with increased expression of *MET* (Fig. 4A, red) and one with *MET* expression levels similar to those of the nonbasal cancers (Fig. 4A, blue). To determine if increased expression of *MET* had functional consequences in these cancers, we generated a gene signature of *MET* activation





**Fig. 5.** High MET staining (score = 3) correlates with ER<sup>-</sup>, ER<sup>-</sup>/ERBB2<sup>-</sup>, and basal cancers. (A) Strong membrane staining and (B) strong cytoplasmic staining of MET observed in breast cancer tissue microarray cores (Magnification: 400×). (C) High MET staining (score = 3) negatively correlates with ER staining ( $P = 0.016$ ). (D) High MET staining (score = 3) negatively correlates with ER and ERBB2 staining ( $P = 0.024$ ). (E) High MET staining (score = 3) significantly associates with the basal subtype by immunohistochemistry ( $P = 0.015$ ).

cancer subtypes. Although MET expression was observed in all subtypes, MET levels  $\geq 2$  were not associated with ER expression, ERBB2 expression, or a specific subtype. However, the highest MET staining (score = 3) was enriched in ER<sup>-</sup> and ER<sup>-</sup>/ERBB2<sup>-</sup> cancers (Fig. 5C and D and Table S6). Furthermore, high MET expression (MET = 3) correlated with the basal immunohistochemical subtype (Fig. 5E and Table S6). These findings show that MET is expressed in the majority of breast cancers and highest levels of MET are present more frequently in aggressive subtypes.

## Discussion

Several studies have demonstrated that Met and HGF/SF are associated with poor prognosis in breast cancer ([www.vai.org/metandcancer](http://www.vai.org/metandcancer)), but we still have a limited understanding for how and when Met influences mammary tumorigenesis. Here, we report that mutationally activated Met on the FVB/N background is able to induce a high incidence of diverse breast carcinomas in a knockin mouse model. Other mouse studies support the tumorigenic effect that Met activation has on the mammary epithelium (15, 27). In this issue, Ponzio et al. describe a transgenic model of mutationally activated Met that develops mammary carcinomas (28). The development of diverse histological phenotypes with basal characteristics in both models suggests that Met may initiate tumorigenesis in an early progenitor cell. This is contrary to the conventional thought of Met primarily being involved in the later stages of tumor progression but consistent with the Wang et al. transgenic hepatocellular carcinoma model (29). Met<sup>mut</sup> mice require both mutation and

Met amplification for the development of aggressive mammary cancers, yet MET has not been shown to be mutated or amplified in human breast cancer. We hypothesize that Met<sup>mut</sup> bypasses the genetic instability required for sporadic human breast cancer and genetic amplification is key to the high penetrance observed in the mouse.

Understanding the signaling pathways that drive tumorigenic growth in the absence of hormone and ErbB2 signaling is critical for the development of effective therapies. Several reports indicate that up-regulation of growth factor signaling pathways may compensate for decreased estrogen and progesterone signaling (2). More recent work has shown that MET amplification occurs in lung cancers that develop resistance to gefitinib or erlotinib treatment (30). Met<sup>mut</sup> mammary tumors are ER<sup>+</sup>/PR<sup>-</sup>, suggesting that Met activation may overcome decreased hormone signaling. In addition, high MET expression was associated with ER<sup>-</sup>/ERBB2<sup>-</sup> human breast cancers. These results corroborate the finding in human breast cancers that MET is a prognostic factor independent of ERBB2 and suggest that MET signaling may be a critical component for driving tumor progression in the absence of ER, PR, or ERBB2 expression.

Molecular subtypes of breast cancer have given us a new understanding of factors that affect prognosis, yet our comprehension of these subtypes is still somewhat limited to their hormone receptor and ERBB2 status. Recent work has connected EGFR and CK5 expression to the basal subtype, but an independent predictor has not been defined (31). More likely, several genes will be needed to predict each subtype. This is the first report of a receptor tyrosine kinase mouse model that develops tumors with basal characteristics. In addition, we demonstrate that high MET expression is associated with human basal cancers. These results are strongly supported by both the mouse model and the human breast cancer analysis reported by Ponzio et al. Importantly, these studies indicate that MET may serve as a therapeutic target for those patients with the most aggressive tumors and currently the fewest therapeutic options.

## Methods

**Survival Curves.** Survival was determined using the Kaplan and Meier survival function. Pairwise comparisons of survival curves were done using a log-rank test.

**Tumor Analysis.** Mice were examined biweekly for tumor development and euthanized when tumors were between 1 and 2 cm<sup>3</sup>. Tumor samples were surgically isolated and fixed in 4% paraformaldehyde/PBS for 24 h. Fixed tissues were dehydrated, paraffin-embedded, and cut into 5- $\mu$ m sections. Experiments using mice were approved by the Van Andel Research Institute Institutional Animal Care and Use Committee.

**Met FISH.** Interphase FISH was performed on tumor touch preparations as described in ref. 14. Detailed procedures are provided in the *SI Methods*.

**Immunohistochemical Analysis.** Antigen retrieval and detection were performed using a Discovery XT (Ventana Medical Systems). Detailed procedures are provided in the *SI Methods*.

**Breast Tissue Microarray Construction and Immunohistochemical Subtype Scoring.** Human breast tissue microarrays consisting of duplicate 0.6-mm cores (Beecher Instruments) were constructed from archival tumor blocks from 137 patients with invasive breast cancer after surgical intervention at Washington University and Barnes-Jewish Hospital in St. Louis from 1997 to 2003. Immunohistochemistry for ER, PR, EGFR, Ck5/6, and HER2 and FISH for HER2 were performed as described in refs. 21 and 26. Detailed procedures are provided in the *SI Methods*.

**Gene Expression Analysis.** Detailed procedures are provided in the *SI Methods*.

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