Evaluation of Biomarkers in Multiple Ipsilateral Synchronous Invasive Breast Carcinomas

Pooja Navale, MD; Ira J. Bleiweiss, MD; Shabnam Jaffer, MD; Anupma Nayak, MBBS, MD

- Context.—The College of American Pathologists guidelines recommend testing additional tumor foci in multifocal invasive breast carcinomas for the biomarkers estrogen receptor (ER), progesterone receptor, and HER2 only if the carcinomas show different morphologies or grades.

- Objective.—To assess clinical significance of testing for biomarkers in additional tumor foci in multifocal invasive breast tumors.

- Design.—Retrospective analysis of 118 patients diagnosed with ipsilateral synchronous multifocal breast carcinomas from January 2015 through March 2016 at Mount Sinai Hospital (New York, New York).

- Results.—Eighty-six cases were tested for at least 1 of the 3 biomarkers in additional tumor foci. Fifteen cases (17%) showed discordant staining between the 2 foci for at least one biomarker. Of the 7 of 67 ER-discordant cases (10%), 4 (57%) showed major variation from negative to positive, and in 3 cases with major discordance, the index tumor was negative for progesterone receptor, whereas a smaller focus was positive. A difference in HER2 expression was noted in 5 of 86 cases (6%). In only 5 of the 15 patients (33%) with discordant results, biomarker testing on additional foci would have been offered per the College of American Pathologists recommendations because of differences in histology or grading. Of the remaining 10 patients, 7 (70%) with positive results on smaller foci would have been deprived of appropriate adjuvant systemic treatment if the smaller focus had not been tested.

- Conclusions.—We propose that negative values expressed in the primary tumor be repeated routinely on additional ipsilateral synchronous tumors.

(Arch Pathol Lab Med. 2019;143:190–196; doi: 10.5858/arpa.2017-0494-OA)

The American Joint Committee on Cancer (AJCC) defines multifocal invasive breast tumors as “multiple simultaneous ipsilateral carcinomas that can be unambiguously demonstrated to be macroscopically distinct and measurable using available clinical and pathological techniques.”1 The detection of multifocal and multicentric breast cancers has increased, given the advances in imaging techniques in recent years.2–4 Despite that increasing prevalence, the prognostic and management implications of multifocal breast carcinoma are uncertain and a subject of debate.5–13 Furthermore, the clonal and biologic relationship between different foci is not well understood; whether multiple foci are derived from a single cancer clone or arise as independent synchronous primary tumors is still a subject for discussion.14,15

Current College of American Pathologists (CAP) guidelines recommend characterizing prognostic and predictive biomarkers (estrogen receptor [ER], progesterone receptor [PR], and HER2 status) only in the largest tumor focus unless the grade and/or histology of additional, smaller tumor foci are markedly different.16 The evolving data on tumor heterogeneity in breast cancers however suggest that approach should be questioned.17 At our institution, we have observed a recent increase in clinical requests for testing of additional foci especially if the tested tumor focus (the largest) is negative for 1 of the 3 biomarkers. The purpose of this study was to assess the clinical significance of testing additional tumor foci for biomarkers (ER/PR/HER2) in a multifocal setting.

MATERIALS AND METHODS

This was a retrospective data analysis of multifocal breast carcinoma cases retrieved from the surgical pathology database of the Mount Sinai Hospital (New York, New York) between January 2015 and March 2016, under approval by the institutional review board. All cases fulfilled the current AJCC definition of multifocal lesions. Each patient’s clinical and pathologic data, including age, gender, specimen type (biopsy or excision), number of invasive foci, tumor size, histologic tumor type and grade, presence of lymphatic invasion, and ER/PR/HER2 status, were recorded. In addition, ER (clone SP1), PR (clone 1E2), and HER2 (clone 4B5) (Ventana

Accepted for publication April 11, 2018.
Published online September 7, 2018.
From the Department of Pathology, Mount Sinai Hospital and Icahn School of Medicine, New York, New York. Drs Bleiweiss and Nayak are now with the the Department of Pathology and Laboratory Medicine, Perelman School of Medicine & Hospital, University of Pennsylvania, Philadelphia.
The authors have no relevant financial interest in the products or companies described in this article.
Presented in part at the annual meeting of the United States and Canadian Academy of Pathology; March 15, 2016; Seattle, Washington.
Corresponding author: Anupma Nayak, MBBS, MD, Department of Pathology and Laboratory Medicine, Perelman School of Medicine & Hospital, University of Pennsylvania, Founders 6.045, 3400 Spruce St, Philadelphia, PA 19104 (email: Anupma.nayak@uphs.upenn.edu).
Table 1. Histologic Features of the Largest Tumor Focus in 118 Cases of Multifocal Breast Carcinoma

| Characteristic Result |
|-----------------------|
| Age, y, mean (range) 58 (33–88) |
| Tumor foci, No. (%) 2 82 (69) ≥3 36 (31) |
| Size, cm, mean (range) 1.6 (0.1–3.5) |
| Histology, No. (%) IDC 72 (61) ILC 14 (12) Mixed 22 (19) Other 10 (8) |
| Grade, No. (%) Well differentiated 14 (12) Moderately differentiated 46 (39) Poorly differentiated 58 (49) |
| Positive staining, No. (%)a ER 97 (82) PR 87 (74) HER2 16 (14) |
| Additional foci, No. (%) Dissimilar histology 25 (21) Dissimilar grade 17 (14) |

Abbreviations: ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PR, progesterone receptor.

a Some tumors were positive for more than one stain.

RESULTS

Of 800 newly diagnosed invasive cancer cases between January 2015 and March 2016, 118 (15%) were classified as multifocal with an age range of 33 to 88 years (mean, 58 years). Eighty-two of those cases (69%) had 2 foci whereas 36 (31%) had 3 or more invasive foci. Sixty-six cases (56%) had diagnoses of multifocal lesions on core biopsy and in the remaining 52 cases (44%) multifocality was detected on surgical specimens. The largest tumor focus ranged from 0.1 cm to 3.5 cm (mean, 1.6 cm) in size. The histologic features and biomarker profile of the largest tumor foci are listed in Table 1. Additional tumor foci were histologically dissimilar in 42 of the 118 cases (36%), either by type (25 of 118; 21%) or by histologic grade (17 of 118; 14%). Additional IHC testing on smaller foci was performed in 86 cases (73%), including 67 (57%) of the 118 cases that stained positively for ER protein, 67 cases (57%) for PR protein, and 86 cases (73%) for HER2/neu oncoprotein. Of note, only the biomarker with a negative value in the larger focus was repeated in the smaller focus. In cases with more than 2 foci, the tumor with the worse histologic grade was selected for additional testing; however, in cases with identical histology and grade, the second largest focus of tumor was selected for additional testing.

Of the 86 cases, 15 (17%) showed a discordant staining pattern between the index tumor and smaller tumor foci (Table 2). Regarding ER expression, 7 of 67 cases (10.4%) showed a discordant staining pattern between the index tumor and additional smaller tumor focus. Four of the 7 cases (57%) had a major discordance in staining from negative (0%) to positive expression (100%, 100%, 95%, and 25%), whereas the remaining 3 cases converted from negative (0%) to low positive (1%, 2%, and 5%). In 3 of the 4 cases (75%) with major discordance, the smaller tumor focus was strongly positive for ER, whereas the index tumor was negative (cases 2, 3, and 5). Conversely, one case (case 7) was positive for ER in the index tumor but negative in the additional smaller focus. Of note, in 3 cases with major discordance (cases 2, 3, and 7), individual tumor foci were dissimilar by histologic grade and/or type.

For PR expression, 7 of 67 cases (10.4%) showed discordant staining between the index tumor and smaller foci. Four cases had major variations in PR scoring from negative (0% or <1%) to positive expression (70%, 20%, 80%, and 60%), and 3 had minor discordance from negative (0%) to low positive (2%, 2%, and 10%). In 3 of 4 cases (75%) with major discordance (cases 3, 8, and 9), the index tumor was negative for PR, whereas a smaller focus was positive. One case (case 10) was positive for PR in the index tumor but was negative in the additional smaller focus. In 3 cases (cases 3, 9, and 10), individual tumor foci were dissimilar in histology, and 2 of those (66%) had additional differences in grade. Two cases had additional changes in ER status; none had additional changes in HER2 status.

Five of 86 cases (6%) showed changes in HER2 status from negative to positive either by IHC (n = 4; 80%) or fluorescence in situ hybridization assay (n = 1; 20%) when tested on additional smaller foci. All 5 HER2-discordant cases (100%) had additional foci of similar histology. Only 1 case (case 7; 20%) had a difference in histologic grade (2 versus 3) between multiple foci. Two cases had additional changes in ER status; none had a change in PR status.

DISCUSSION

The clinical and therapeutic significance of intertumoral heterogeneity in multifocal breast carcinomas is not well addressed in the literature. A few studies15,18–24 that have...
reported results of testing multiple ipsilateral tumor foci for ER/PR/HER2 status have yielded disparate results (Table 3). Middleton et al\(^\text{15}\) observed identical ER/PR/HER2 staining pattern in 14 of 32 multicentric cases (44%), in which additional tumor foci were also tested for biomarkers. The authors therefore suggested that multicentric tumors possibly arise from intramammary spread of a single clone of tumor cells. Similarly, Garimella et al\(^\text{18}\), in their pilot study of 18 cases, reported no variation in ER expression despite the variability in the histologic grade of tumors. Variation in PR expression was however observed in 2 of 18 cases (11%), but that did not influence clinical management.

### Table 2. Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2 Staining Patterns of Index Tumor (Site 1) and Smaller Focus (Site 2) in 15 Discordant Cases

| Case No. | Age, y | Laterality | Site | Histology | SBR | IHC Positivity, % | HER2 FISH Result |
|---------|-------|-----------|------|-----------|-----|------------------|------------------|
| 1       | 46    | R         | 1    | IDC       | 9   | 0 0 0            |                  |
| 2       | 68    | L         | 1    | IDC       | 9   | 1 60 0           |                  |
| 3       | 71    | L         | 1    | IDC       | 9   | 0 <1 0           |                  |
| 4       | 71    | L         | 1    | IDC       | 8   | 0 0 0            |                  |
| 5       | 60    | L         | 1    | IDC       | 9   | 0 0 0            |                  |
| 6       | 52    | R         | 1    | IDC       | 8   | <1 0 0           |                  |
| 7       | 51    | R         | 1    | IDC       | 6   | 100 5 0          |                  |
| 8       | 49    | R         | 1    | Mixed     | 8   | 30 <1 3+        | Positive         |
| 9       | 60    | R         | 1    | IDC       | 8   | 90 0 0           |                  |
| 10      | 53    | L         | 1    | Mixed     | 6   | 100 60 2+        | Negative         |
| 11      | 53    | L         | 1    | IDC       | 8   | 90 2 3+         |                  |
| 12      | 48    | R         | 1    | ILC       | 7   | 80 85 0          |                  |
| 13      | 62    | R         | 1    | ILC       | 8   | 95 90 3+        | Equivocal        |
| 14      | 54    | R         | 1    | ILC       | 7   | 95 90 3+        | Positive         |
| 15      | 56    | R         | 1    | IDC       | 8   | 100 90 3+       |                  |

Abbreviations: FISH, fluorescence in situ hybridization; IDC, invasive ductal carcinoma; IHC, immunohistochemistry; ILC, invasive lobular carcinoma; NA, data not available; SBR, Scarff-Bloom-Richardson score.

### Table 3. Discordance in Biomarker Status Reported by Previous Studies When Additional Tumor Foci Were Tested Along With the Index Tumor

| Source | ER | PR | HER2 | Recommendation |
|--------|----|----|------|----------------|
| Middleton et al\(^\text{15}\), 2002, n = 14 | 0 (0) | 0 (0) | 0 (0) | No |
| Garimella et al\(^\text{18}\), 2007, n = 18 | 0 (0) | 2 (11) | NA | No |
| Choi et al\(^\text{19}\), 2012, n = 65 | 2 (3) | 7 (11) | 4 (6) | No |
| Bethune et al\(^\text{20}\), 2013, n = 246 | NA | NA | 16 (7) | No |
| Buggi et al\(^\text{21}\), 2012, n = 113 | 5 (4) | 18 (16) | 11 (10) | Yes |
| Pekar et al\(^\text{22}\), 2014, n = 110 | 4 (4) | 1 (1) | 7 (6) | Yes |
| Boros et al\(^\text{23}\), 2014, n = 155 | 18 (12) | 29 (19) | 25 (16) | Yes |
| East et al\(^\text{24}\), 2015, n = 70 | 2 (3) | NA | 6 (9) | No |
| Present study, 2018 | 7 of 67 (10) | 7 of 67 (10) | 5 of 86 (6) | Yes |

Abbreviations: ER, estrogen receptor; NA, data not available; PR, progesterone receptor.
because the 2 cases were ER+. Choi and colleagues\textsuperscript{19} studied 65 cases of multifocal breast cancer and found differing ER status in 2 (3%), differing PR status in 7 (11%), and differing HER2 status in 4 (6%); however, the variation in staining was associated with differences in histologic features, high histologic and nuclear grade, p53 overexpression, and the presence of a heterogeneous ductal carcinoma in situ component. The authors concluded that multifocal, invasive carcinomas of the breast usually have a single phenotype and analysis of the index tumor for biomarkers was sufficient in most cases in routine practice; however, in cases associated with any of the above-mentioned features, additional tumor foci should be evaluated separately for biomarkers. Bethune et al\textsuperscript{20} investigated only the HER2 status in a series of 246 multifocal tumors. HER2 status was concordant between multiple foci in 230 cases (93.5%), with the largest focus having the most positive HER2 results in 242 cases (98.4%). None of their cases (0%) revealed greater HER2 positivity in the smaller focus, unless that focus was either of a higher grade or histologically different. Those authors supported the evaluation of HER2 on the largest focus, with additional testing on smaller foci if it was a different histologic type or a higher grade.

Figure 1. Case 5 with a larger tumor focus of invasive, poorly differentiated ductal carcinoma (A), with adjacent, lymphatic tumor emboli (B, arrows). C. Larger tumor focus was negative for estrogen receptor, progesterone receptor, and HER2 expression. D, Lymphatic tumor emboli (arrows) are strongly positive for HER2 oncprotein expression (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]; original magnification ×200 [C and D]).
In contrast, Buggi and colleagues, in their prospective analysis of 113 multifocal cases with identical histology, found 2 cases (1.7%) with ER positivity, 10 cases (8.8%) with PR positivity, and 4 cases (3.5%) with HER2 gene-amplified in the smaller focus but negative in the index tumor. Those authors concluded that the standard approach to the analysis of multiple tumors would have prevented adequate adjuvant treatment (hormonal, anti-HER2, and chemotherapy) in at least 12% (14 of 113) of their patient cohort.

Another recent study by Pekar et al reported similar findings, with 8 out of 110 patients (7.3%) exhibiting phenotypic heterogeneity of therapeutic significance in microscopically identical tumor foci in terms of histologic type and grade. Furthermore, patients with phenotypically different multifocal tumors had shorter survival times. The largest study so far, in this context by Boros et al, also concluded that assessment of all tumor foci would have selected 19 of 155 cases (12.25%) to receive different adjuvant treatments compared with what would have been indicated if only the biologic status of the largest primary tumor was assessed.

Our results are in line with Buggi et al, Pekar et al, and Boros et al and do not support the current recommendation by the CAP of characterizing only the largest tumor.
focus by ER, PR, and HER2 testing. As stated, 15 of 86 patients (17%) in our cohort had discordance in ER, PR, or HER2 status when tested additionally on smaller foci, including 3 patients (20%) with discordance in ER status, 5 (33%) patients with discordance in PR status, 3 (20%) of those 15 patients with discordance in HER2 status, 2 (13%) with discordance in ER and PR status, and 2 (13%) with discordance in ER and HER2 status. In only 5 of the 15 patients (33%; cases 2, 3, 7, 9, and 10) would biomarker testing on additional foci have been offered per the current CAP recommendations because of differences in histology or grading between the larger and smaller foci. Of the remaining 10 cases with histologically identical tumor foci, 7 (70%) with positive test results on smaller foci would have been deprived from receiving appropriate adjuvant systemic treatment if the smaller focus would not have been tested. Noteworthy are 4 of the 15 patients (27%) who became eligible for anti-HER2 therapy.

Case 5 in our study is worth describing in detail (Figures 1, A through D, and 2, A through B). Two separate masses (at the 11-o’clock and 2-o’clock positions in right breast) that were suspicious for malignancy were detected on imaging in this patient. Core biopsies from the 2 masses demonstrated histologically identical, invasive, poorly differentiated duct carcinoma (grade 3), with associated lymphatic invasion (Figures 1, A, and 2, A). The biomarker testing was initially performed on the biopsy in the 11-o’clock position from the larger-sized tumor. That tumor was negative for ER (0%; Figure 1, B), PR (0%; Figure 1, C), and HER2 expression (score 0; Figure 1, D); however, the lymphatic tumor emboli associated with the tumor were strongly positive for HER2 (Figure 1, D). That prompted us to do biomarker testing on the second focus. Additional testing of the second tumor focus (in the 2-o’clock position) revealed weak to moderate staining for ER (25%) and strong staining for HER2 (score 3+) (Figure 2, C and D, respectively). Interestingly, the lymphatic tumor emboli adjacent to the second tumor were negative for ER, PR, and HER2 (Figure 2, E). This case is a perfect example of intertumoral, immunophenotypic heterogeneity, a phenomenon also well documented at the genomic level and a plausible explanation for therapeutic failure and poor survival outcome in individual patients with breast cancer. A recent study by Desmedt and colleagues29 highlights the interlesional, genomic heterogeneity in multifocal breast cancers. The authors studied molecular characteristics of 36 multifocal breast cancers with similar histology (ductal), grade, and ER and HER2 status. Gene sequencing with a panel of 360 cancer-related genes revealed that in many patients (12 of 36; 33%) multifocal tumors did not share any substitutions/indels with the interlesion heterogeneity observed for oncogenic mutations in genes, including PIK3CA, TP53, GATA3, and PTEN.

Multifocality in breast cancer is associated with increased axillary nodal metastases and a potentially worse outcome, with increased risk of local relapse, when compared with unifocal cancer.5 Considering our data and similar findings from other recent studies, it would not be unreasonable to consider that an unfavorable prognosis for patients with multifocal cancer was somehow linked to current practices of inadequate immunohistochemical characterization of individual tumor foci resulting in inadequate adjuvant systemic treatment. One may argue that testing all tumor foci for all 3 biomarkers (ER, PR, and HER2) may not be cost effective, particularly with increasingly strict regulations for test reimbursement. To contain costs, we therefore recommend repeating only the biomarker(s) with initially negative value(s) on the additional smaller foci. That approach would at least ensure that no patient was deprived of available targeted therapies, with minimal increase in diagnostic costs.

To conclude, our study is one of the few studies evaluating the clinical utility of biomarker testing in additional tumor foci in multifocal breast carcinomas. Our data highlight the benefits of additional testing on smaller tumor foci for the biomarker not expressed in the index tumor, regardless of the tumor histology. Current CAP recommendations for biomarker testing in the multifocal setting should be revisited.

References
1. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual—Part VII, Breast. 7th ed. New York, NY: Springer; 2010:347–376.
2. Sardanelli F, Giuseppe GM, Panizza P, et al; Italian Trial for Breast MR in Multifocal/Multicentric Cancer. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. Am J Radiol. 2004;183(4):1149–1152.
3. Wilkinson LS, Gwin-Wilson R, Hall T, Potts H, Sharma AK, Smith E. Increasing the diagnosis of multifocal primary breast cancer by the use of bilateral whole-breast ultrasound. Clin Radiol. 2005;60(5):573–578.
4. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008;26(19):3248–3258.
5. Vera-Badillo FE, Napoleon M, Ocana A, et al. Effect of multifocality and multicentricity on outcome in early stage breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;146(2):235–244.
6. Andea AA, Wallis T, Newman LA, et al. Pathologic analysis of tumor size and lymph node status in multifocal/multicentric breast cancer. Cancer. 2002;94(5):1383–1390.
7. Counsell SJ, Boyages J. Multifocal and multicentric breast cancer: does each focus matter [published correction appears in J Clin Oncol. 2006;24(10):1648]? J Clin Oncol. 2005;23(30):7497–7502.
8. Weissenbacher TM, Zschage M, Janni W, et al. Multifocal and multicentric versus unifocal breast cancer: is the tumor-node-metastasis classification justified? Breast Cancer Res Treat. 2010;122(1):27–34.
9. Tot T, Gere M, Pékár G, et al. Breast cancer multifocality, disease extent and survival. Hum Pathol. 2011;42(11):1761–1769.
10. Ustunelugu BO, Bicic A, Seidl U, et al. The importance of multifocal/multicentric breast cancer on the disease-free survival of breast cancer patients. Am J Clin Oncol. 2012;35(6):580–586.
11. Chung AP, Huynh K, Kidner T, Mirzadehgan P, Sim MS, Giuliano AE. Comparison of outcomes of breast conserving therapy in multifocal and unifocal invasive breast cancer. J Am Coll Surg. 2012;215(1):137–146.
12. Lim W, Park E-H, Choi S-L, et al. Multicentric and multicentric breast cancer: does each focus matter? [published correction appears in J Clin Oncol. 2006;24(10):1648]. J Clin Oncol. 2005;23(30):7497–7502.
13. Gentilini O, Bottini E, Roimens N, et al. Conservative surgery in patients with multifocal/multicentric breast cancer. Breast Cancer Res Treat. 2009;113(3):577–583.
14. Dawson PJ, Baekey PA, Clark RA. Mechanisms of multifocal breast cancer: an immunocytochemical study. Hum Pathol. 1995;26(9):963–969.
15. Middleton LP, Vlastos G, Mirza NQ, Eva S, Sahin AA. Multicentric mammary carcinoma: evidence of monoclonal proliferation. Cancer. 2002;94(7):1910–1916.
16. Lester SC, Rose S, Chen YY, et al. Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med. 2009;133(10):1515–1538.
17. Almendro V, Fuster G. Heterogeneity of breast cancer: etiology and clinical relevance. Clin Transl Oncol. 2011;13(11):767–773.
18. Garamella V, Long ED, O’Kane SL, Drew PJ, Cawkell L, Oestrogen and progesterone receptor status of individual foci in multifocal invasive ductal breast cancer. Acta Oncol. 2007;46(2):204–207.
19. Choi Y, Kim EJ, Seol H, et al. The hormone receptor, human epidermal growth factor receptor 2, and molecular subtype status of individual tumor foci in multifocal/multicentric invasive ductal carcinoma of breast. Hum Pathol. 2013;43(1):48–55.
20. Bethune GC, Mullen JB, Chang MC. HER2 testing of multifocal invasive breast carcinomas: How many blocks are enough? Am J Clin Pathol. 2013;140(4):588–592.
21. Buggi F, Folli S, Cuciccia A, et al. Multicentric/multifocal breast cancer with a single histotype: is the biological characterization of all individual foci justified? Ann Oncol. 2012;23(8):2042–2046.
22. Pekar G, Gere M, Tarjan M, Hellberg D, Tot T. Molecular phenotype of the foci in multifocal invasive breast carcinomas: intertumoral heterogeneity is related to shorter survival and may influence the choice of therapy. Cancer. 2014;120(1):26–34.

23. Boros M, Ilyes A, Nechifor Boila A, Moldovan C, Eniu A, Stolnicu S. Morphologic and molecular subtype status of individual tumor foci in multiple breast carcinoma: a study of 155 cases with analysis of 463 tumor foci. Hum Pathol. 2014;45(2):409–416.

24. East EG, Pang JC, Kidwell KM, Jorns JM Utility of estrogen receptor, progesterone receptor, and HER-2/neu analysis of multiple foci in multifocal ipsilateral invasive breast carcinoma. Am J Clin Pathol. 2015;144(6):952–959.

25. Desmedt C, Fumaçalli D, Pietri E, et al. Uncovering the genomic heterogeneity of multifocal breast cancer. J Pathol. 2015;236(4):457–466.