GUEST EDITORIAL

Next-Generation Breast Cancer Omics

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Breast cancer is complex and now recognized as a diverse collection of neoplastic diseases of the breast with distinct molecular characteristics^{1,2} and clinical outcomes.^{3–5} The realization that breast cancer represents multiple disease states with diverse molecular underpinnings is directly attributable to the application of omic technologies to investigations of this pathology. Beyond patient-to-patient variations in breast cancer presentation and survival,⁶ the breast cancer tissue itself from any given patient is complex (Figure 1A). Disease tissue consists of neoplastic breast epithelial cells, tumor-associated fibroblasts, various infiltrating immune cells, normal tissue components (vascular supply and extracellular matrix), and adjacent (normal or abnormal) nonneoplastic cells (Figure 1B). Hence, breast cancers reflect a complex tissue microenvironment where multiple factors might influence biological characteristics and clinical behaviors.

Omic technologies and approaches enable important questions to be addressed at the level of cells, tissues, organ systems, and the intact organism. Investigation of breast cancer at each of these levels is important to expansion of our overall understanding of these diseases (and cancer in general).⁷ As depicted in Figure 1C, genomics, transcriptomics, proteomics, and epigenomics are typically applied to cells and tissues to interrogate cell-specific characteristics, including DNA sequence variations or gene expression patterns, and/or to examine the influences of cellular interactions, such as cell-cell, cell-matrix, and cell-milieu, on the biology of breast cancer. Given the presence of multiple cell populations within a breast cancer and its adjacent nonneoplastic tissue, there are several cellular targets for examination using omics. Other omics can be applied at multiple or all levels encompassing cells, tissues, organ systems, and the organism. These omics include metabolomics, which is the study of metabolism and metabolites, and

interactomics, which examines the complex interactions of various molecules influencing intracellular or intercellular processes. These omic approaches are areas of active study in breast cancer. There is little question that breast cancer and other neoplastic diseases can be influenced by systemic factors present in tissue settings, at the primary site in the breast and at various sites of metastasis. Ultimately, using information derived from various omic technologies and approaches, we will begin to understand the phenomics of breast cancer. Phenomics is concerned with phenotypes expressed in the organism (or cells and tissues thereof) that result from underlying molecular features and complex interactions.⁸

This special Breast Cancer Theme Issue of *The American Journal of Pathology* includes seven reviews covering major topics related to next-generation breast cancer omics, what has been learned from these approaches during the past decade or more, and where these technologies will take the field of breast cancer research in the coming years. In many/most cases, next-generation omic technologies are being used in the investigation of basic science questions related to breast cancer. Such studies are expanding our basic understanding of the multiple diseases that are termed breast cancer, their causes, molecular pathogenesis, and consequences. However, these studies are also identifying new molecular targets and pathways for therapy⁹ and/or are exploiting molecular findings for new predictive biomarkers that can be used to develop companion diagnostics.¹⁰ Translation of the basic science findings into practical applications and clinical

Accepted for publication July 27, 2017.

Disclosures: None declared.

W.B.C. is Special Editor of the Breast Cancer Theme Issue.

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Figure 1 Breast cancer complexity, cellular heterogeneity, and omics. **A:** Hematoxylin and eosin–stained section of a breast cancer demonstrating neoplastic breast epithelial cells interspersed with extracellular matrix, cancer-associated fibroblasts, and infiltrating immune cells. **B:** Schematic illustrating the various constituents of a breast cancer that contribute to cancer heterogeneity. Neoplastic cells (white) are admixed with cancer-associated fibroblasts (orange), and infiltrating immune cell types (pink, green, and light blue). Adjacent to this cancerous mass would be nonneoplastic (normal or abnormal) epithelium and stroma. The breast cancer mass has a blood supply (dark blue) consisting of normal blood vessels and contains extracellular matrix components (red). **C:** Application of omic technologies and approaches at cellular, tissue, organ system, and organismal levels. Original magnification, $\times 20$.

utility represents the ultimate goal of breast cancer research based on next-generation omic technologies and approaches.¹¹ This collection of reviews provides the reader with information emerging from basic science research, observations from clinical research, and developments from applied research related to the current state of next-generation breast cancer omic technologies and approaches.

Genomics represents the study of the genome: the entire DNA sequence, organization of genetic material, and functional consequences of sequence variations. Marotti et al¹² discuss the use of next-generation sequencing to investigate the genomics of triple-negative breast cancer and the utility of this approach for identification of new molecular targets with clinical importance. Eventually, this approach may become practical for assessment of specific panels of genetic biomarkers in individual patients, providing guidance for therapeutic intervention. Geyer et al¹³ present an overview of triple-negative breast cancer and the multiple disease entities that compose this clinical classification of breast neoplasia. With greater understanding of the molecular underpinnings of triple-negative breast cancer subtypes, more effective clinical management strategies using conventional and targeted therapies will emerge.

Transcriptomics refers to the study of the transcriptome: the entire expressed genome as RNA, including expression of structural genes and other functional RNA species. Russnes et al¹⁴ describe the use of transcriptomic approaches to classify and subclassify breast cancers based on gene expression signatures, and the evolution of methods for molecular classification of disease. With continued investigation in this area, new methods for molecular classification of breast cancer will be developed that will find practical utility in the clinical workup of individual patients, providing improved prognostication of their disease and guidance for therapy. Epigenomics reflects the study of the epigenome, including DNA methylation, histone modifications, chromatin

organization, and functional interactions that influence gene expression. Davalos et al¹⁵ present an overview of breast cancer epigenomics and how our expanding understanding of epigenetic mechanisms is improving our basic understanding of the molecular pathogenesis of breast cancer, identifying new epigenetic biomarkers and new therapeutic targets.

Proteomics is the study of the proteome, including all of the proteins expressed in a given cell type, and structure and function of those proteins. Mardamshina and Geiger¹⁶ provide a discussion of next-generation breast cancer proteomic approaches and their application to research and clinical testing. Proteomics represents a technological approach to the assessment of breast cancer that may find practical clinical utility because noninvasive sources of biomarkers (from blood or other sources) can often be used in lieu of tissue samples, making this approach desirable for patient testing.

Rosenbaum and Weisman¹⁷ discuss the exploitation of molecular biomarkers for development of companion diagnostics with clinical utility in breast cancer treatment. Companion diagnostics with good testing characteristics (sensitivity and specificity) are essential for the advancement of personalized medicine in the treatment of breast cancer, identifying which patients will or will not benefit from a given treatment (or providing prognostication in the same manner). Coleman and Anders¹⁸ describe the use of various gene expression signatures for classification of breast cancer and for prediction of probability of relapse and responses to therapy. With expansion of breast cancer clinical trials using various combinations of traditional chemotherapeutic drugs and newer targeted drugs (and/or with radiotherapy and immunotherapy), large cohorts of patients are being observed for clinical outcome measures that can be coupled with patient-specific molecular information to identify new molecular signatures (based on gene expression patterns and/or gene mutations) that predict therapeutic responses. In some cases, these molecular signatures will be translated into practical clinical diagnostics.

References

1. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D: Molecular portraits of human breast tumours. *Nature* 2000, 406:747–752
2. The Cancer Genome Atlas Network: Comprehensive molecular portraits of human breast tumours. *Nature* 2012, 490:61–70
3. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Lonning PE, Borresen-Dale AL: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001, 98:10869–10874
4. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, Parrish M, Atsma D, Witteveen A, Glas A, Delahaye L, van der Velde T, Bartelink H, Rodenhuis S, Rutgers ET, Friend SH, Bernards R: A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002, 347:1999–2009
5. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH: Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 2002, 415:530–536
6. Rivenbark AG, O'Connor SM, Coleman WB: Molecular and cellular heterogeneity in breast cancer: challenges for personalized medicine. *Am J Pathol* 2013, 183:1113–1124
7. Liu ET: Functional genomics of cancer. *Curr Opin Genet Dev* 2008, 18:251–256
8. Houle D, Govindaraju DR, Omholt S: Phenomics: the next challenge. *Nat Rev Genet* 2010, 11:855–866
9. Mohamed A, Krajewski K, Cakar B, Ma CX: Targeted therapy for breast cancer. *Am J Pathol* 2013, 183:1096–1112
10. De Abreu FB, Wells WA, Tsongalis GJ: The merging role of the molecular diagnostics laboratory in breast cancer personalized medicine. *Am J Pathol* 2013, 183:1075–1083
11. Miquel-Cases A, Schouten PC, Steuten LMG, Retel VP, Linn SC, van Harten WH: (Very) early technology assessment and translation of predictive biomarkers in breast cancer. *Cancer Treat Rev* 2017, 52:117–127
12. Marotti JD, de Abreu FB, Wells WA, Tsongalis GJ: Triple-negative breast cancer: next generation sequencing for target identification. *Am J Pathol* 2017, 187:2133–2138
13. Geyer FC, Pareja F, Weigelt B, Rakha E, Ellis IO, Schnitt SJ, Reis-Filho JS: The spectrum of triple-negative breast disease: high- and low-grade lesions. *Am J Pathol* 2017, 187:2139–2151
14. Russnes HG, Lingjaerde OC, Borresen-Dale A-L, Caldas C: Breast cancer molecular stratification: from intrinsic subtypes to integrative clusters. *Am J Pathol* 2017, 187:2152–2162
15. Davalos V, Martinez-Cardus A, Esteller M: The epigenomic revolution in breast cancer: from single-gene to genome-wide next-generation approaches. *Am J Pathol* 2017, 187:2163–2174
16. Mardamshina M, Geiger T: Next generation proteomics and its application to clinical breast cancer research. *Am J Pathol* 2017, 187:2175–2184
17. Rosenbaum JN, Weisman P: The evolving role of companion diagnostics for breast cancer in an era of next-generation omics. *Am J Pathol* 2017, 187:2185–2198
18. Coleman WB, Anders CK: Discerning clinical responses in breast cancer based upon molecular signatures. *Am J Pathol* 2017, 187:2199–2207