Personalized medicine, individualized medicine, and precision medicine are interchangeable terms that describe an approach to the treatment of disease that harnesses our understanding of the molecular basis and mechanisms of a given disease and matches appropriate therapeutic interventions. Breast cancer represents a diverse collection of malignant diseases of the breast with highly variable clinical behaviors and disparate responses to therapy. The perplexing challenge of patient management for the clinician is reflected in the observation that among breast cancer patients with similar disease (based on traditional histopathological measures) and similar therapeutic strategy, some patients will be cured (and thereafter live a normal lifespan) whereas others will progress to premature death. In fact, we now recognize that breast cancer is tremendously complex in its molecular pathogenesis, natural history, and biology.

Breast cancer affects not only women but also men (1% of cases). It occurs both as sporadic malignant disease and as hereditary disease. Hereditary breast cancers manifest in patients with strong genetic predisposition involving BRCA1 and BRCA2 genes, as well as in patients with familial cancer syndromes involving other genes, such as TP53. Most breast cancers occur in women without identifiable risk factors, and strong hereditary predisposition accounts for only 5% to 10% of cases. Often, the genetic component of disease predisposition may reflect small but measurable risks associated with polymorphic sequence variations at multiple loci. Breast cancer occurs in both young and old patients, and affects people of all races and ethnicities. Numerous other risk factors are associated with breast cancer development, including reproductive factors, dietary factors, obesity, and environmental exposure. Beyond the highly variable nature of breast cancer etiology, the malignant disease is also highly complex. Recent studies have dissected the molecular biology of clinical breast cancers through detailed analysis of genomics (gene mutations and copy number variations), transcriptomics (expression of structural genes and non-coding RNAs), epigenomics (DNA methylation and histone modifications), and proteomics (changes in protein expression and functionality). These studies have revealed immense diversity in individual breast cancers and across cohorts of breast cancer patients. The emerging picture of the molecular biology of breast cancer suggests that there are few dominant driver mutations reflecting specific genes or pathways as a required event leading to tumorigenesis. Rather, there are numerous driver or passenger mutations in a given breast cancer, as well as epigenetic alterations that significantly impact the expression of individual genes and the overall gene expression signature. Ultimately, the clinical behavior of a given breast cancer reflects its unique combination of activating and inactivating genetic mutations and epigenetic alterations that give rise to cancer-associated phenotypes (eg, uncontrolled cell proliferation, loss of cellular differentiation, local invasiveness, and ability to spread to distant tissue sites).

Personalized medicine for the routine clinical management of breast cancer patients is a lofty goal that will require expansion of our knowledge of the molecular underpinnings of this disease and its various subtypes. With increased investigation of the genomics, transcriptomics, epigenomics, and proteomics of breast cancer, our understanding of the mechanisms that drive the development and progression of this group of diseases will expand. In addition, new molecular targets for drug therapy may be identified, and new biomarkers may emerge that are useful in breast cancer detection, prognostication, and therapy guidance. Basic
science research represents the foundation for breast cancer personalized medicine, cataloging the molecular alterations and characterizing their effects on breast tumorigenesis and progression. Applied science will harness the information generated related to the biology of breast cancer to select genes and pathways for development of targeted therapies and innovative drug designs and to investigate practical biomarkers for clinical management. Equally important are clinical studies that provide insight into patient outcomes (both disease-free and long-term survival) in response to specific therapeutic strategies with consideration of the molecular characteristics of the breast cancer and of the patient. Utilization of currently available technologies in investigational studies that span basic, applied, and clinical sciences will elucidate the molecular underpinnings of breast cancer biology and how the character of individual breast cancers influence outcomes. Even if the critical molecular events are linked with patient responses to therapy in breast cancer, challenges will remain with respect to the implementation of personalized medicine in the clinical setting.8

This special Breast Cancer Theme Issue of The American Journal of Pathology includes seven reviews covering major topics related to the molecular pathogenesis of breast cancer and implications for personalized breast cancer therapy. Ghoussaini et al9 provide an overview of the genetics of breast cancer susceptibility, including discussion of both rare high-penetrance alleles (ie, BRCA1 and BRCA2) and common low-penetrance alleles, many of which are newly identified. The involvement of these common low-penetrance alleles and combinations thereof is extremely important as these alleles may be involved in many sporadic breast cancers. Stefansson and Esteller10 present a comprehensive review of breast cancer epigenetics. Epigenetics holds significant implications for breast cancer treatment reflecting the importance of gene expression signatures to breast cancer biology as well as recognizing that epigenetic alterations are reversible and may provide the basis for new therapeutic approaches. Engebraaten et al11 review our current understanding of triple-negative breast cancers and potential new targets for therapy that might improve disease-free and long-term outcomes of patients afflicted by these difficult-to-treat breast cancers. De Abreu et al12 describe the state of the art in breast cancer molecular diagnostics and the importance of the clinical diagnostics laboratory in realizing personalized breast cancer medicine. Marino et al13 discuss progression of breast cancer to metastatic disease, the molecular evolution occurring during this process, and implications for prevention of metastasis or treatment in the individual patient. Mohamed et al14 provide a comprehensive examination of targeted therapies that are currently used in the treatment of breast cancer and studies on the identification of novel molecular targets for breast cancer drug development. Rivenbark et al15 discuss methods for classification of breast cancer, correspondence among methods, and the extensive diversity that exist among breast cancers based on molecular data. This review goes on to discuss how breast cancer heterogeneity impinges on accurate classification of disease and implications for realization of true personalized breast cancer therapy. This collection of reviews provides the reader with information from basic research, observations from clinical research, and developments from applied research related to the past, present, and future of breast cancer personalized medicine.

References