Prognosis and Prediction in Breast Cancer: Is There a Need for Further Tests?

Olaf G. Wilhelm[1]* and Marion Kiechle[2]

Paradigm shifts in diagnostic and therapeutic approaches in breast cancer substantially improved survival and quality of life. Since 1989 until 2015, the mortality rate decreased by 39% according to US breast cancer statistics (*1*). The first paradigm shift occurred once it was recognized that breast cancer is not a local but rather a systemic disease. Veronesi and coworkers demonstrated in a ground-breaking trial that breast-conserving surgery instead of mutilating radical mastectomy does not impact survival (*2*). The next paradigm shift emerged with the understanding that clinicopathological factors such as the axillary lymph node status, tumor size, incidence of metastases, and grade of cellular differentiation have prognostic value, which led to the introduction of adjuvant chemotherapy to reduce and prevent disease recurrence. Subsequently, the knowledge of the importance of the estrogen receptor (ER) not only identified patients with better overall survival but also led to the first targeted therapy approach, which blocked the estrogen receptor pathway (*3*). Further subtyping was enabled through the discovery of the human epidermal growth factor 2 (HER2) receptor by Slamon and coworkers (*4*). At the beginning of the new millennium, Perou et al. introduced intrinsic subtyping in the molecular pathology of breast cancer (*5*). Shortly thereafter, Sørlie and coworkers defined the molecular subtypes Luminal A, Luminal B, basal-like, and HER2-enriched and demonstrated the very different prognosis for overall survival and disease-free survival (*6*).

The obviously heterogeneous nature of breast cancer triggered the next key challenge: how to provide the optimum management and treatment for each and every patient diagnosed with this disease. Predictive factors foretell the probability of response of a cancer patient to a specific anticancer therapy. Determination of ER, progesterone receptor, and HER2 has become mandatory for predicting response to endocrine or to HER2-directed therapy before administration of (neo)adjuvant anticancer drugs. For example, adjuvant endocrine treatment of ER-positive breast cancer patients with tamoxifen reduced disease recurrence rates by about 40%, whereas ER-negative patients failed to benefit from such treatment (*7*).

Different from that, prognostic factors provide information about the future course of the disease (disease-free and overall survival) of patients not treated with anticancer therapeutics. It is crucial in breast cancer patient management to determine the aggressiveness of the tumor, i.e. how do we gain information about the probability of disease recurrence and to identify those patients in need for systemic treatment. Following this line of thoughts, Jänicke and coworkers (*8*) demonstrated that increased concentrations of either one or

[1]Therawis Diagnostics GmbH, Munich, Germany; [2]Department of Obstetrics and Gynecology, University Hospital Rechts der Isar, Technical University Munich, Germany.
***Address correspondence to this author at:** Grillparzerstrasse 14, 81675 Munich, Germany. Fax +49-89-4142455740; e-mail olaf.wilhelm@therawis.com.
DOI: 10.1373/jalm.2018.026161

[3] **Nonstandard abbreviations:** ER, estrogen receptor; HER2, HER2neu; TNBC, triple-negative breast cancer.

both uPA and/or PAI-1 in the primary tumor correlate with cancer aggressiveness and poor outcome independent of ER, HER2, or progesterone receptor expression. Low-risk lymph node-negative patients, according to the uPA/PAI-1 status (uPA and PAI-1 low), may be spared the burden of adjuvant chemotherapy because of their excellent prognosis, whereas high-risk patients derive enhanced benefit from adjuvant chemotherapy. The clinical value of the uPA/PAI-1 status (high or low) has been evaluated in retrospective and different prospective multicenter clinical trials, including a meta-analysis conducted by the EORTC Receptor and Biomarker Group, comprising 8377 breast cancer patients from 18 independent studies and collectives (*9*). Finally, the prognostic and predictive impact of uPA/PAI-1 was validated with the highest level of evidence (LoE 1A). The 10-year data of the prospective multicenter Chemo N0-trial confirmed that patients of the low-risk group without adjuvant chemotherapy had a low risk of recurrence (*10*). This uPA/PAI-1 ELISA, commercially available as FEMTELLE® (BioMedica Diagnostics), is a prognostic test for node-negative, early-stage breast cancer patients.

Defining intrinsic subtypes and gene expression has substantially improved the understanding of the biological diversity and heterogeneity of breast cancer. Especially in ER-positive and HER2-negative patients, a reliable estimation of the risk of disease recurrence is crucial to select the appropriate (neo)adjuvant therapy. Commercially available gene signatures such as Endopredict® (Myriad Genetics Inc.), OncotypeDX® (Genomic Health Inc.), Mammaprint® (Agendia Inc.), PAM50 (Nanostring Technologies Inc.), IHC4 score, or the Breast Cancer Index (Biotheranostics Inc.) have been developed to serve this purpose and are highly valuable to identify patients who could be spared chemotherapy and who are sufficiently treated with endocrine therapy alone (*11*). The American Society of Clinical Oncology has provided thorough clinical practice recommendations for the use of biomarkers to guide decisions on adjuvant systemic therapy for early breast cancer (*12*). However, none of these assays delivered sufficient evidence to be of predictive value and are not recommended to be used to guide systemic chemotherapy (*12*). Furthermore, miRNA has increasingly attracted attention. The stable miRNA is easily detectable and quantifiable and has demonstrated clinical utility as prognostic and predictive biomarkers, not only in breast cancer (*13*).

A major challenge for any prognostic and predictive strategy represents the intratumor heterogeneity. This heterogeneity within each individual tumor entity occurs not only on a morphologic level but also on a DNA, RNA, and protein level and may change over the course of the disease (*14*). The initial mutations of the primary tumor may no longer be responsible for tumor recurrence, or an initial biomarker-negative tumor may develop into a biomarker-positive tumor. To overcome these obstacles, sequencing technologies may be applied at diagnosis, followed by monitoring to identify drivers of tumor progression and therapy resistance. If tumor tissue is not accessible, the disease can be monitored by introducing standardized analysis of a biofluid sample, e.g., liquid biopsy. Liquid biopsy allows for repeated sampling to monitor changes of the disease, which leads to progression and resistance. Three approaches are currently intensively investigated: circulating tumor cells, circulating DNA, and exosomes (*15*).

To further improve outcome of breast cancer patients, 3 areas where prognostic and predictive tests would be of high clinical value are envisioned: first, the broad molecular heterogeneity of triple-negative breast cancer (TNBC) has hindered the discovery of effective biomarkers to tailor chemotherapy at an individual level. Various studies suggested that TNBC consists of several subtypes and, thus, does require subtype-specific therapy based on its biological characteristics. To further characterize TNBC on a molecular level, various subtypes

have been proposed, with some differences in the number of subtypes or classifying methods; the clinical relevance of the TNBC-subtypes, however, is not yet defined (*16*). Second, Luminal A disease is treated with endocrine therapy according to guidelines. However, endocrine therapy such as ER antagonists is accompanied with significant toxic effects. Up to 3% of patients develop secondary cancers such as endometrial cancer, and up to 6% of patients will experience life-threating thromboembolism. Therefore, a prognostic test that identifies Luminal A patients with excellent prognosis could spare a patient subpopulation from receiving endocrine therapy. Third, postsurgical adjuvant therapy and presurgical neoadjuvant cancer therapy, which apply endocrine therapy, immunotherapy, and chemotherapy, have been shown to improve disease-free and overall survival in early-stage breast cancer patients. Predictive markers indicate response or resistance to a specific medical treatment. For any specific type of cancer, it is common knowledge that only a portion of patients will respond to a particular treatment, whereas others are likely to suffer from adverse side effects without benefit. In the case of breast cancer, various patients may respond differently to chemotherapy and/or endocrine therapy. In the absence of predictive markers, the one-dose/treatment-fits-all approach is misguided. Such predictive factors to identify patients who benefit or do not benefit from certain therapies are of high medical need. Recently, the PITX2 DNA-methylation assay was introduced into the market; it represents the first marker to predict the outcome to anthracycline-based chemotherapy (*17*, *18*), considered standard-of-care systemic treatment in early breast cancer patients. Nevertheless, we still do face a demand for individualized systemic treatment of breast cancer patients. Especially, there is still an unmet need to predict the necessity, efficacy, and potential toxic side effects of drugs and the outcome of breast cancer patients under therapy—and thus quality of life—while also avoiding high treatment-related costs and unnecessary chemotherapy or endocrine therapy.

The advances in the treatment of breast cancer are impressive, and patient- and tumor-tailored strategies delivered on their promises. Nevertheless, breast cancer is not only a medical problem but also an economic and social challenge, which could be overcome by further efforts from academia and the pharmaceutical and medical drug/device industry, potentially leading to new treatment modalities in the framework of personalized cancer medicine. Molecular diagnostic tests, which can predict response of a breast cancer patient to a certain cancer drug, are highly needed but are, unfortunately, in short supply.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form.* **Employment or Leadership:** O.G. Wilhelm, Therawis Diagnostics GmbH. **Consultant or Advisory Role:** None declared. **Stock Ownership:** O.G. Wilhelm, Therawis Diagnostics GmbH. **Honoraria:** None declared. **Research Funding:** None declared. **Expert Testimony:** None declared. **Patents:** None declared.

Acknowledgments: Dedicated to and in memory of Prof. Dr. rer. nat. Dr. med. habil. Manfred Schmitt.

REFERENCES

1. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics 2017, racial disparity in mortality by state. CA Cancer J Clin 2017;67:439–48.
2. Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 1981;305:6–11.
3. Ward HW. Anti-oestrogen therapy for breast cancer: a trial of tamoxifen at two dose levels. BMJ 1973;1:13–14.
4. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244: 707–12.
5. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.
6. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001;98:10869–74.
7. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771–84.
8. Jänicke F, Schmitt M, Pache L, Ulm K, Harbeck N, Höfler H, Graeff H. Urokinase (uPA) and its inhibitor PAI-1 are strong and independent prognostic factors in node-negative breast cancer. Breast Cancer Research and Treatment 1993;24:195–208.
9. Look MP, van Putten W, Duffy MJ, Harbeck N, Christensen J, Thomssen C, et al. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. J Natl Cancer Inst 2002;94:116–28.
10. Harbeck N, Schmitt M, Meisner C, Friedel C, Untch M, Schmidt M, et al. Chemo-N 0 Study Group. Ten-year analysis of the prospective multicentre Chemo-N0 trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. Eur J Cancer 2013;49:1825–35.
11. Schmidt M, Thomssen C, Untch M. Intrinsic subtypes of primary breast cancer - gene expression analysis. Oncol Res Treat 2016;39:102–10.
12. Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016;34:1134–50.
13. Smith B, Agarval P, and Bhowmick NA. MicroRNA applications for prostate, ovarian and breast cancer in the era of precision medicine. Endocr Relat Cancer 2017; 24:R157–72.
14. Turashvili G, Brogi E. Tumor heterogeneity in breast cancer. Front Med (Lausanne) 2017;4:227.
15. Brock G, Castellanos-Rizaldos E, Hu L, Coticchia C, and Skog J. Liquid biopsy for cancer screening, patient stratification and monitoring. Transl Cancer Res 2015;4: 280–90.
16. Ahn SG, Kim SJ, Kim C, Jeong J. Molecular classification of triple-negative breast cancer. J Breast Cancer 2016;19: 223–30.
17. Hartmann O, Spyratos F, Harbeck N, Dietrich D, Fassbender A, Schmitt M, et al. DNA methylation markers predict outcome in node-positive, estrogen receptor-positive breast cancer with adjuvant anthracycline-based chemotherapy. Clin Cancer Res 2009;15:315–23.
18. Aubele M, Schmitt M, Napieralski R, Paepke S, Ettl J, Absmaier M, et al. The predictive value of PITX2 DNA methylation for high-risk breast cancer therapy: current guidelines, medical needs, and challenges. Dis Markers 2017;2017:4934608.